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A SYMPOSIUM OF POLISH MEDICAL CONTRIBUTIONS IN WORLD WAR II

LUDWIK ANIGSTEIN*

FOREWORD

During the summer of 1946 I was privileged to participate with a distinguished group of colleagues on a medical teaching mission to Poland for the United Nations Relief and Rehabilitation Administration. It was peculiarly moving to me to revisit the medical schools, hospitals, and research institutions which had developed so well in Poland following World War I. With destruction and ruin all about them, our Polish colleagues had continued, with amazing fortitude, to carry forward medical research.

Our mission found a prevailing enthusiastic spirit among the medical workers of Poland in the face of every conceivable severe handicap. Libraries were destroyed, and medical periodicals were unobtainable. Equipment and facilities were primitive. Nevertheless, research was continued underground during the war years by surviving scientists, many of whom suffered from starvation and disease, and most of whom labored under constant threat of penalty of death for their scientific efforts.

Under these circumstances it is astonishing that any medical contributions could have been assembled during World War II by Polish medical scientists. Nevertheless, our Polish colleagues approached us with requests that we help them find an opportunity for the publication of some of the observations which they had made during the war years, and which they thought might be of interest also to the scientist abroad. The six contributions comprising this symposium are offered as an example of the type of medical research which was carried on in Poland during the trying period of World War II. The authors are endeavoring to continue their studies in the limited facilities available to them.

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LEUKERGY: CLUMPING OF WHITE BLOOD CELLS IN CYTOLOGICALLY HOMOGENOUS GROUPS, A NEW PHENOMENON OF INFLAMMATION*

LUDWIK FLECK AND ZOFIA MURCZYNSKA

If we allow citrated blood to stand in a test tube, the white cells which settle slower than the red cells, will accumulate in the upper layer of the column. The sedimentation of the platelets is still slower, these appearing usually above the leukocytes. Centrifugation at low speed of the leukocyte layer may help to concentrate and separate them from platelets.

After incubation at 37° C., samples of leukocyte suspension removed at half hour or hourly intervals, show that the formerly scattered leukocytes accumulate in increasing groups. In normal blood, the process is very slow (3–5 hours) and involves only a small portion of white cells or may be hardly visible. However in the course of different infectious diseases (typhus, typhoid, pneumonia, sepsis) or in animals injected with killed bacteria or turpentine the process is intensified and we see shortly after the blood was taken, almost all the leukocytes clumped in groups of 8 to 20 cells.

For microscopic examination a drop of the cell suspension is placed on a slide, slightly agitated and stained with Pappenheim's stain, after cautious hemolysis by distilled water (see photomicrographs). The majority of the groups are cytologically homogenous: they are formed of neutrophiles, lymphocytes or monocytes. Large lymphocytes as well as small ones agglomerate in separate groups. Eosinophiles in scarlet fever form homogenous groups even if their number amounts only to 5 or 7 per cent. Mixed groups may sometimes be seen, but, as a rule, the lymphocytes or the neutrophiles form in such a group a separate pole or an included island. A single monocyte or lymphocyte may be found in a group of 8–10 leukocytes, but the cytological homogeneity is a marked and characteristic feature.

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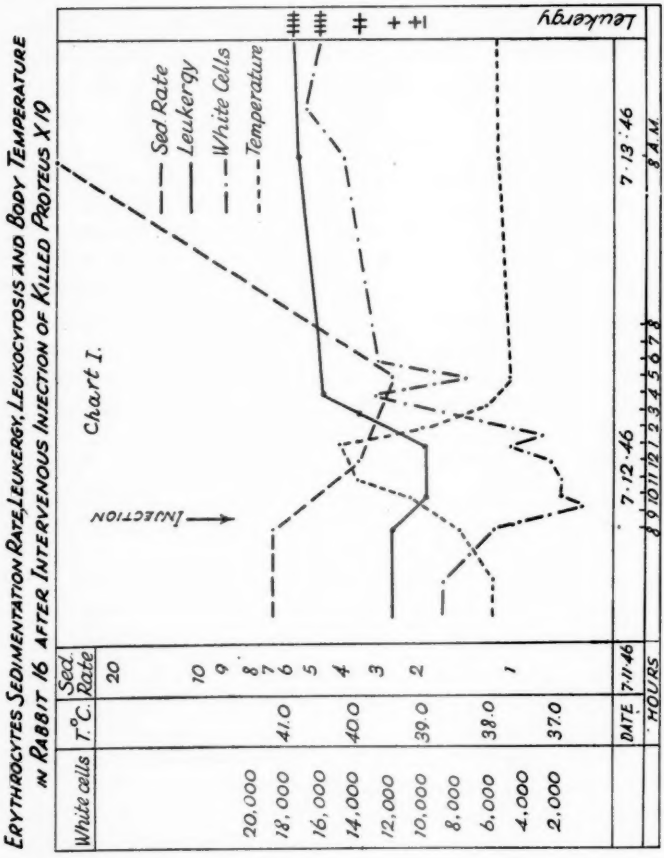
The phenomenon of autoagglutination of platelets in normal blood is well known; it vanishes in thrombopathy (Morawitz and Brugsch, 1933). It increases in inflammatory processes, with white cells either absent or present in the agglutinated platelets. White cells may form a wreath around a group of platelets (almost exclusively lymphocytes, seldom neutrophiles, practically never monocytes). In other cases, the platelets surround a group of neutrophiles. In some cases, the agglutination of platelets is independent of the clumping of white cells. These pictures seem to be characteristic for different clinical entities. In typhus, we find a remarkable clumping of monocytes, with the eosinophiles clumping during convalescence. In typhoid fever, there is more clumping of lymphocytes than of neutrophiles. In malaria during the attack a strong agglutination of platelets surrounded by lymphocytes and separate groups of neutrophiles free from platelets were seen. These pictures remind us of the thrombocytobarine reaction (Rieckenberg-Kriczewski), especially the wreath surrounding the groups of neutrophilic leukocytes.

The phenomenon of agglomeration of white blood cells in cytologically homogeneous groups, found for the first time by one of us (Fleck) in 1942 has been termed *leukergy*.

The occurrence of increased leukergy in infectious diseases and in experimental inflammation (e.g., with turpentine), indicates that the phenomenon is linked with inflammation, persisting for some time during the stage of convalescence (7–14 days). Observations on animals indicate a high sensitivity of this phenomenon. Repeated heart punctures for withdrawal of blood samples from normal animals induce an increased leukergy, and the same effect can be produced by repeated intraperitoneal injections of sterile physiological saline. In spite of the relationship of leukergy to inflammation, it is still uncertain whether a very slight agglomeration of leukocytes should be looked upon as normal, or as a sign of clinically imperceptible inflammation.

The course of leukergy in rabbits after an intravenous injection of killed bacteria (Proteus X19) is represented in Chart I and Table 1. The degree of leukergy is recorded by



microscopic examination after 1, 2, 3, or 4 hours incubation of the blood. The symbol ± indicates only a very few groups; + indicates groups of 3–4 among the scattered majority; ++ indicates the state when about 50 per cent of the leukocytes are agglomerated in groups of 3–5 cells; later the majority of cells clump to groups of 6–10 cells +++; finally, all the leukocytes with very few exceptions are agglomerated in large groups of 6–15 cells ++++.

TABLE 1

Figures illustrating Chart 1

Day	Time	Temp. C°	White Cells Per mm.	Erythrocyte Sed. Rate in 2 Hrs. mm.	Leukergy
7.10	9.00	38.5	7,000	2.75	+
7.11	9.00	38.0	9,000	7.00	+
7.12	8.30	38.5	5,600	2.25	+
	8.50	0.5cc of a suspension of killed B. proteus X19 i.v.			
	9.15		2,500		
	9.45		1,500		
	10.15	39.2	2,500		±
	10.45		2,700		
	11.30	+0.1	2,900		±
	12.00		2,500	3.5	
	1.00	40.2	4,600		
	1.30	39.0	3,000	3.0	++
	2.30		4,400		
	3.30	38.1	10,100		
	4.15		13,500	2.5	+++
	5.30	37.8	7,600		
	6.00		13,000		
7.13	8.30	38.0	15,000	23.0	++++
	11.30		18,000		
7.14	9.00	38.3	14,000	45.0	++++
7.15	9.00	38.4	10,500	22.0	++++
7.16	9.00			7.0	++
7.18	9.00	38.6	5,000	2.0	±

Our experiments show that a leukopenia immediately follows injection (20–30 minutes) with a count of about 2,000; after several hours the white cell count rises to 15,000 or more, and then drops after 24 hours to normal. The body temperature rises within 2–3 hours following injection to 40°–41° C. depending on the dose given. After remaining at this level for several hours, the temperature returns to normal. The sedimentation rate increases after 24 hours, and returns to normal after 3–4 days. Increased leukergy appears after the leukopenic phase, before leukocytosis, at the height of fever or after its drop, but preceding the increased sedimentation rate. Increased leukergy persists longer than fever, or the accelerated sedimentation rate, and usually longer than the leukocytosis.

If we inject intrapleurally into rabbits 0.5–1 ml. of turpentine we obtain the next day a serous or blood stained exudate.

A marked leukergy with only slight leukocytosis is observed, which may or may not be accompanied by fever. The increased leukergy persists for 5–7 days, sometimes with no increase of sedimentation rate (Table 2).

TABLE 2

Showing Reactions in Rabbits After Injection of Killed Bacteria. Turpentine and Normal Saline

Rabbit No.	Day	Temp. C°	White Cells	Erythrocyte Sed. Rate in 2 Hrs. mm.	Leukergy
1	11.6	38.4	9,900	2.0	+
	11.7				
	9.15	intravenous injection of killed B. proteus X19			
	12.30	39.8	5,200	1.5	±
	11.8	38.2	17,000	3.5	++++
	11.9	36.8	8,300	5.0	++++
	11.10	37.2	7,300	8.0	++++
	11.12	36.7	7,600	4.0	++
	11.13	37.5	8,800	2.0	±
	11.20	37.2	9,700	2.0	±
		intravenous injection of killed B. proteus X19			
	11.21	37.2	7,000	15.0	++++
	11.22	36.8	9,000	2.0	+++
	11.23	37.0		3.0	++++
	11.26	38.3	6,300	2.0	++
		intravenous injection of killed B. proteus X19			
	11.27	36.8	8,000	7.0	++++
	11.30	37.0	13,000	5.0	++
17	7.10		9,000		++
		intrapleural injection of 1 ml. turpentine			
	7.11	39.1	12,000	2.0	++++
	7.12	38.3	13,000	2.5	+++
	7.15	38.3	11,000		+++
	7.22	intrapleural injection of 1 ml. turpentine			
	7.23	38.3	7,600		++++
	7.24				++++
19	6.5				±
	6.6	intrapleural injection of 200 ml. saline			
	6.7				++++

Observations on a hanging drop of citrated blood or of the leukocyte layer of citrated blood on a heated microscope stage, show that the process of leukergy passes through several phases: at first the primarily scattered leukocytes begin to accumulate in different parts of the preparation. They still remain scattered for the most part, but the concentration of the cells in some places is already visible. They exhibit active ameboid movement, or a passive brownian movement induced

by platelets, and by the rouleaux formation of erythrocytes. These various passive movements bring the leukocytes progressively closer together, the oscillations contributing to their contact. The process may be accelerated by shaking or by short exposure to heat over 40° C. which causes a transient disintegration of the rouleaux. Amoeboid movement, while bringing leukocytes nearer to each other, may also separate those already grouped, since the agglomeration of leukocytes is largely independent of ameboid movement. This first phase of movement is followed by clumping of adhering cells. Newly formed groups may still disintegrate; later, the adhesive forces increase. Leukocytes move from the periphery of a group to its center passing one over the other; the group shrinks, takes the shape of a mulberry and is surrounded by a clear space, free of leukocytes. These clumped leukocytes, still active, extend pseudopodia, and may move as a group in one direction. In general, a group does not disintegrate, but cases were observed where several clumped cells left the group and moved away.

In cases of increased leukergy, agglomeration may be accomplished in 10 to 20 minutes; sometimes white clumps of leukocytes may be seen sticking to the wall of an inclined test tube immediately after the blood has been collected and mixed with sodium citrate. In blood samples showing slight leukergy, the whole process is slow—3 to 5 hours.

Strong agglutination of platelets enhances the clumping of leukocytes, the latter being attached to clumps of platelets. Lymphocytes are seldom involved. In principle, the agglomeration of leukocytes is independent from the agglomeration of plate' , and proceeds as well in preparations without platelets.

The optimal temperature for the process of leukergy is 37°–40° C. Lower temperature slows the process, but it may be found at +2° C. It seems that with the decrease of temperature, the clumping of lymphocytes becomes more marked, whereas higher temperature favors the clumping of neutrophils. The clumping is weaker in temperatures over 40° C. and when 46° C. is reached, the clumps may partially disintegrate.

The transfer of leukocytes from an inflammatory process into normal serum or plasma does not inhibit the agglomeration. Blood from an inflammatory source was diluted immediately after withdrawal, 1–5 with normal plasma. It was then centrifuged, the corpuscles washed twice with normal plasma and suspended in normal plasma. The agglomeration of the leukocytes was not affected. In cases of extremely strong leukergy the phenomenon may be noticed immediately after the withdrawal of blood even without sodium citrate in the thick blood films stained as previously described. We must therefore conclude that leukocytes from an inflammatory process possess in vivo the tendency to agglomerate. Leukocytes of healthy animals transferred into plasma from a case of inflammation, do not show increased clumping as a rule, the phenomenon appearing only in rare instances (Table 3). Normal leukocytes transferred into pleural exudates obtained subsequent to pleural injection of turpentine show sometimes a remarkable clumping.

Agglomeration may also be demonstrated in leukocytes from a peritoneal effusion elicited by the method of de Haan; the leukocytes concentrated in the liquid by centrifugation at low speed and containing only white cells without erythrocytes or platelets, may often be leukergic, however this is not a constant phenomenon. We observed rabbits with highly increased leukergy in the blood, with no leukergy from the leukocytes of the peritoneal cavity; on the other hand, leukergy of the peritoneal leukocytes without blood leukergy was never observed. Progressive dilutions of leukergic or negative serum mixed with a suspension of leukocytes from the peritoneal fluid of such a case as last described, show agglomeration of leukocytes in clumps of varying size decreasing with the dilution of the serum. Highly leukergic serum gives clumping in dilutions from 1–160 to 1–200. The less effective normal serum acts in 1–20 to 1–80. The factor causing agglomeration of the leukocytes from the peritoneal cavity is thermostabile. Serum diluted 1–5 and heated for 30 minutes in a water bath at 96° C. is still active and may only show a slightly decreased titer as compared with the unheated serum (Table 3).

TABLE 3

Clumping of Leukocytes from Peritoneal Effusions in Rabbit Serum

Leukocytes	Serum	Clumping in Serum Dilutions 1:10	1:20	1:40	1:80	1:160	1:320	Remarks	Leukocytes in Physiol. Saline (Control)
	Rabb. 10								
Rabbit 10	leukergy	++	++	++	++	±	—	active serum	
Blood Leukergy	+++	+++	+++	++	+	±	—	inactivated	±
+++	Rabb. 4								
	leukergy	++	++	±	±	±	—	active serum	
	+	++	++	+	±	±	—	inactivated	—
	Rabb. 20	++	++	++	++	±	—	active serum	
Rabbit 10	leukergy	+++	+++	++	—	±	—	inactivated	
Blood Leukergy	Rabb. 14								±
+++	leukergy	++	++	±	±	±	—	active serum	
	+	++	++	+	±	±	—	inactivated	
	Rabb. 12								
Rabbit 13	leukergy	+++	+++	+++	+++	++	—	active serum	
Blood Leukergy	+++	+++	+++	+++	+++	±	—	heated 96 C.	+
+++	Rabb. 14								
	leukergy	+++	+++	+++	+++	+	—	active serum	
	+	+++	+++	+++	++	—	—	heated 96 C.	
	Rabb. 13								
Rabbit 13	leukergy	++	++	++	++	++	+	active serum	
Blood Leukergy	+++								+
+++	Rabb. 4								
	leukergy	++	++	++	+	±	—	active serum	
	±								

Exudates obtained subsequent to intrapleural injection of turpentine (0.5–1.0 ml.) into rabbits agglomerate leukocytes from peritoneal effusions into large clumps sticking to the bottom of the test tube with clear supernatant fluid. After some time, the leukocytes swell and eventually disintegrate. The degree of agglomeration diminishes with the dilution of the exudate, the maximum effective dilution being 1–600. Thus exudates, more active than the serum, cause not only agglomeration but also disintegration of leukocytes.

By comparison of leukergy with the phenomenon of autoagglutination of platelets, arrangement of red cells in rouleaux, erythrocyte sedimentation or cold agglutination of erythrocytes, it is evident that, although a distinct phenomenon, it has a close relationship. In inflammatory processes, leukergy seems to be a more sensitive test than the erythrocyte sedimentation reaction, but it is less sensitive than the agglutination of platelets which depends to a great degree on temperature, medium, and method of collecting the blood. Platelets clump rather in the refrigerator, leukocytes in the incubator. A comparison of parallel blood specimens kept in the incubator and in the refrigerator shows the independence of the agglutination of the platelets and the leukocytes.

The agglutination of platelets is according to Morawitz and Brugsch a serological phenomenon, and the active substance may be specifically absorbed from the plasma. Attempts to absorb from serum or plasma the active factor in leukergy give no clear result, as yet, since blood leukocytes are not suitable for the test, these in general not clumping in leukergic plasma. Leukocytes from peritoneal effusions could be used, but it is not sure whether the clumping of such leukocytes represents the same phenomenon as the agglomeration of leukocytes in leukergic blood, especially since normal plasma or serum heated to 96° C. is almost as active as leukergic blood.

Discussion and Summary

White blood cells in inflammatory processes have a tendency to agglomerate in cytologically homogeneous groups (leukergy). Although demonstrated in vitro, in varying incuba-

tion periods, the leukocytes are already altered in vivo (leukergic) in such a way that immediate washing and suspending in normal plasma does not alter their agglomerating properties. Since the demonstration of the factor causing leukergy present in plasma from cases of inflammation is only in rare cases possible, we may perhaps assume that it is absorbed by circulating leukocytes or by endothelial cells.

Washed leukocytes from a peritoneal effusion are agglomerated by either normal serum or serum from cases with inflammation. From this we can consider two possible alternatives; either leukocytes from peritoneal effusions are always leukergic, or that the agglomeration of blood leukocytes and those from peritoneal effusions are two different processes. Pleural exudates as a rule cause agglomeration of peritoneal leukocytes and they may in certain cases cause an agglomeration of leukocytes in normal blood.

Studies on inflammation have noted that there is a rearrangement of leukocytes in the capillaries and veins of an inflamed area (Boyd, 1943), and that leukocytes tend to become marginal and adhesive within the vein (Dible and Davie, 1945). Probably endothelial cells become more adhesive also, and the sticking of the leukocytes to the vessel wall is the first step in diapedesis. There is reason to believe that the increased stickiness of the leukocytes favors their diapedesis and migration and may perhaps also influence phagocytosis.

Observations in hanging drop preparation prove that ameboid movement directed by elective chemotaxis has no decisive meaning in the process of leukergy; it even appears to oppose at times the agglomeration of leukocytes. Then, too, at low temperatures when ameboid movement stops or is very slow, leukergy continues to take place. A mutual attraction of leukocytes is noted in the phase of concentration before a direct contact is made. A substance increasing the stickiness of cells might come into action, only after contact has been established. This explains why shaking, centrifugation, heating, formation of rouleaux of erythrocytes and agglutination of platelets increase the velocity of leukocyte agglomeration, giving more opportunity for contact by producing currents and induced movements.

There are some reasons for assuming a serological mechanism of the agglutination type to be active. Topley and Wilson, Duncan, Wiener, Herman and others found that the mixing of two independent agglutinating systems results mostly in homologous aggregates. A suspension of nucleated avian erythrocytes, and mammalian erythrocytes, mixed with the respective homologous agglutinating sera shows the two kinds of erythrocytes agglutinated in separate clumps. Since blood cells possess antigens specific for the different types of cells, a nonprotein antigen of leukocytes, a protein antigen of lymphocytes, a separate protein antigen of platelets and others, it is possible to produce cytospecific antisera for the different types of leukocytes, by immunizing either with pus or with lymph nodes or with leukemic blood. The existence of these antigens creates the basis for assuming a serological mechanism in the formation of cytologically homogeneous groups of leukocytes. Moreover, the fact that a certain temperature favors the agglomeration of a certain type of cells, and that the existence of pathological conditions with prevalent leukergy of one type of cell may be explained easily—if not solely—by assuming the existence of cytospecific autoagglutinins. If so, it is also probable that these agglutinins acting on the bone marrow and other hemopoietic organs may influence the blood picture, characteristic for different pathological conditions.

An additional agent of leukergy, non specific in nature, is the stickiness of leukocytes in inflammation, probably induced by a substance liberated at the site of inflammation.

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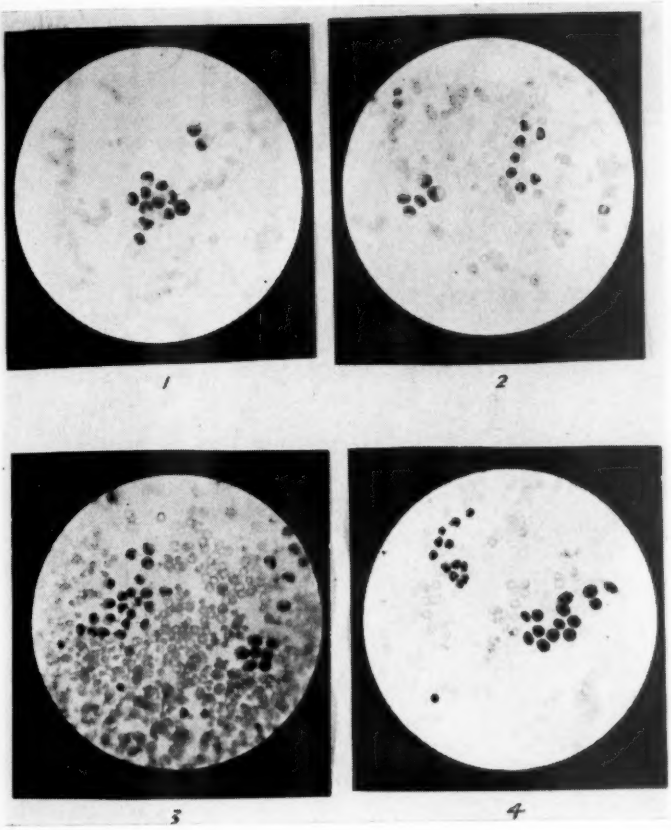
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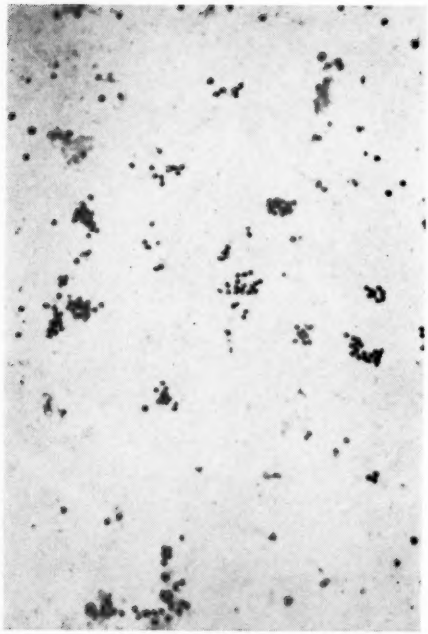

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DESCRIPTION OF PHOTOMICROGRAPHS

1. Leukergy in the blood of a typhus fever patient. Eighth day of disease. A group of mononuclear cells. x 700.
2. The same. Groups of neutrophils and mononuclear cells. x 700.
3. The same. Two groups of cells: 7 lymphocytes and 22 neutrophils. x 700.
4. Leukergy in the blood of a guinea pig, 12 days after typhus infection. Temperature 40.2 C. Two groups: neutrophils and monocytes. x 700.
5. Suspension of leukocytes from a case of typhus fever after 2 hours incubation. x 170.

SPECIFIC ANTIGENIC SUBSTANCES IN THE URINE OF TYPHUS PATIENTS*

LUDWIK FLECK

The search for specific antigenic substances in the urine of typhus patients was initiated in Lwow, 1942, under German occupation. The original plan was to elaborate a test giving earlier diagnosis than the Weil-Felix reaction. The preliminary experiment consisted of injecting a rabbit intravenously with 10 ml. of sterile urine from a case of typhus. The Weil-Felix reaction with the serum of the rabbit became positive to a titer of 1:320. These results encouraged the author to further investigations carried out in collaboration with Drs. Elster, Umschweif, and Anhalt. In addition to elaborating a diagnostic test, it was also thought to utilize the urine of typhus patients as a source of specific antigens for the preparation of a preventive vaccine, very urgently needed at this time.

In May, 1942, the results were reported at a staff meeting of the "Ghetto" Hospital in Lwow, and several months later, the author was deprived of his collaborators who were destroyed by the Germans.

In the present study the following technique was used: in a series of narrow test tubes 1 ml. of typhus serum with a high Weil-Felix titer (1:3,200 or more) undiluted or in dilutions 1:2, 1:3, 1:4, 1:5, was stratified with 1 ml. of clear urine in each tube. A white ring appeared at the plane of junction within a range of 20 minutes. For controls normal urine, normal serum, or urine from cases of other infections than typhus were used. The reaction was very irregular requiring different temperatures. Sometimes the results were better at room temperature, in other cases at 37° C. or 45° C. Some typhus cases were negative. Precipitates were observed occasionally when normal serum and urine from tuberculous patients with a fever were tested. The phenomenon is independent of blood grouping. It may also be produced with

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anti-proteus X19 rabbit serum of high titer. Most likely the variability of the reaction is due to the interference of nonspecific physico-chemical processes, especially since we often found in rabbits inoculated with typhus urine a marked increase in titer for X19 and for *Rickettsia prowazeki*. It was therefore decided to free the urine from unnecessary substances and to concentrate the specific antigen.

The urine used for injection was sterile and therefore free from a possible contamination with X19. It was collected by catheter, left for 48 hours or longer with 0.5% phenol or chloroform, the latter evaporated before use. After the injection of such urine, the agglutination of proteus X19 with the rabbit's serum was of the granular "O" type. Not in every case could typhus antigen be detected by injection into rabbits. It is possible that its presence depends on the severity of the disease, and that urine containing more protein was more active. The specific antigen was found in the urine on the second day of typhus fever. Experiments were carried out as follows: from a group of 38 men coming from an epidemic focus, urine was collected aseptically in sterile bottles, and after addition of chloroform, was kept in the refrigerator. Of this group, 14 persons showed fever several days later, and typhus was diagnosed. From two of these typhus cases, the stored urine was injected into rabbits.

Case 1. Patient R. Fever onset May 20, 1942.
May 27. Rabbit "angora" injected intravenously with 10 ml. of the urine collected 3 days before the onset of the fever.
May 31. Rabbit serum W.F. 1:10 neg.
June 1. Rabbit serum W.F. 1:10 neg.
June 2. Rabbit serum W.F. 1:10 neg. Injection of 10 ml. of urine collected one day before the onset of fever.
June 6. Rabbit serum W.F. 1:40 +.
June 7. Rabbit serum W.F. 1:10 neg. Injection of 10 ml. of urine collected on the second day of fever.
June 9. Injection of 10 ml. of urine collected on the second day of fever.
June 13. Rabbit serum W.F. 1:40 +.
June 14. Rabbit serum W.F. 1:160 +.
June 15. Rabbit serum W.F. 1:160 +.
June 21. Rabbit serum W.F. 1:20 +.
June 22. Rabbit serum W.F. 1:20 +.
June 23. Injection of 10 ml. of urine from the seventh day of fever.

June 24. Injection of 10 ml. of urine from the seventh day of fever, intraperitoneally.
June 29. Rabbit serum W.F. 1:160 +.
June 30. Rabbit serum W.F. 1:320 +.
July 1. Rabbit serum W.F. 1:160 +. Agglutination with *R. prowazeki* 1:160 +.
July 10. Rabbit serum W.F. 1:80 +. Agglutination with *R. prowazeki* 1:80 +.

In this case, the antigen was found on the second day of fever.

In other experiments, the treated rabbits showed titers to 1:640 or even 1:1,280.

In the next series of experiments attempts were made to purify and concentrate the specific antigen. Urine was collected from a group of typhus patients between the third and tenth day of the disease. The following experiments are reported.

Preparation of "K" 20: First, urine was concentrated to one tenth of its volume by evaporation in vacuo, then dialyzed for 48 hours through cellophane against tap water. The liquid was centrifuged, the sediment treated with a small amount of 2/10 N sodium hydroxide, again centrifuged, and added to the main portion from the first centrifugation. The reaction was adjusted to pH6.5, then the preparation was once more evaporated in vacuo to 1/20 of the original volume of urine, and 0.5% phenol added. The obtained preparation was an almost completely clear, brownish fluid containing about 6.6% protein. It showed a slight turbidity with silver nitrate and nitric acid.

July 8, 1942. Precipitin reaction:
Preparation "K" 20 with normal serum: neg.
Preparation "K" 20 with typhus serum: +.
Preparation "K" 20 with physiological salt solution: neg.
July 28. Subcutaneous injection of 0.5 ml. of "K" 20 in a normal rabbit, W.F. 1:10 negative, *R. pr.* 1:20 doubtful ±.
August 2. W.F. 1:80 +; 1:160 ±; *R. pr.* 1:80 +; 1:160 ±.
August 3. W.F. 1:80 +; 1:160 ±; *R. pr.* 1:80 +; 1:160 ±.
August 4. 1:160 +; 1:320 ±; *R. pr.* 1:160 +; 1:320 ±.
August 5. Subcutaneous injection of 0.5 ml. "K" 20 into the same rabbit, and 1.5 ml. one hour later.
August 9. W.F. 1:80 +; 1:160 ±; *R. pr.* 1:160 +; 1:320 ±.
September 10. W.F. 1:160 +; 1:320 ±; *R. pr.* 1:320 +; 1:640 ±.

September 11. W.F. 1:160 +; 1:320 ±; *R. pr.* 1:320 +.
Experiment on human subject (L.F.); August 28, subcutaneous injection of 0.5 ml. of "K" 20; August 29, large area of local edema and redness; August 30, the reaction vanishes.

Preparation of "K" 14: Urine was collected as above, adjusted pH7.0 by hydrochloric acid, concentrated in vacuo to 1/20 of its volume and kept for four days in the refrigerator with 0.5% phenol. The centrifuged sediment was treated for two hours with 50 ml. 2/10N sodium hydroxide, again centrifuged, adjusted to pH7.0 with hydrochloric acid, dialyzed against tap water for 48 hours, again evaporated to 1/20 of the original volume of urine; 0.5% phenol added. The preparation consists of purified substances adsorbed to the original sediment. It is an almost clear substance of a light brown color; specific gravity: 1.037. Protein is practically absent.

Precipitin reaction:
Preparation "K" 14 with normal rabbit serum: neg.
Preparation "K" 14 with typhus serum: +.
Preparation "K" 14 with anti X19 rabbit serum: +.
Preparation "K" 14 with physiological salt solution: neg.
Normal rabbit serum with physiological salt solution: neg.
Rabbit serum anti X19 with physiological salt solution: neg.
Typhus serum with physiological salt solution: neg.

Six days after intravenous injection of 4 ml. of preparation "K" 14 this rabbit showed an increase of anti X19 agglutinins from 1:20 to 1:160. This experiment proves that the sediment contained the antigen and that it can be purified and made free from protein.

The antigen may also be precipitated with ammonium sulfate together with the protein of the urine. With such a preparation, we succeeded in raising the Weil-Felix titer in a rabbit to 1:800 after five injections. Attempts to absorb the antigen to benzoic acid gave uncertain results.

Guinea pigs vaccinated with the preparation "K" 20 and subsequently infected with typhus blood showed no fever, whereas a control guinea pig developed a fever reaction typical for typhus; however, no immunity in guinea pigs against typhus was established.

Preparation "K" 20 was also used as a preventive vaccine for man. The author, his collaborators, and 32 volunteers

were vaccinated. Three injections were administered 0.5, 1.0, and 2.0 ml. subcutaneously. A slight local reaction (tenderness) without general symptoms was noted. The rise of the Weil-Felix titer was in some cases remarkable. Later, 500 people in a concentration camp at Lwow were vaccinated. With few exceptions statistics of the vaccinated were unfortunately lost. Records are available only in regard to the author, his family, and two other persons, all of whom contracted typhus and recovered after a mild or abortive course of the disease. A large number of the vaccinated in the camp did not contract typhus although for several months they were exposed to typhus infections. In contrast, the majority of the nonvaccinated prisoners contracted typhus with a fatality rate of 30%.

Summary and Discussion

An antigenic substance was found in the urine of typhus fever patients, sometimes in the first days of the disease, or in some cases in the last days of incubation. The substance is more frequently found in severe cases, thus making an early uroserological diagnosis of typhus possible. The antigen may be concentrated and purified. Attempts were made to use this antigen as a preventive vaccine. Three liters of urine would provide about 40 doses of vaccine.

With regard to the nature of the described antigenic substances they may be either rickettsiae, or substances liberated from rickettsiae and eliminated by the kidneys. In favor of the first hypothesis is the fact that urinary sediment from typhus patients is infectious for lice. However the amount of the antigenic substance in the urine is too high to assume its origin from eliminated rickettsiae only. The presence of the antigen in the urine separated from the sediment rather indicates a free substance.

The author was unaware of similar observations made independently and at the same time by A. P. Leon in Mexico. (The precipitation of anti-typhus serum by the urine of typhus patients: a new serological test for typhus fever. Rev. Inst. Salubr. y Enferm. Trop., 1942, 3:201–208).

METHODS OF EVALUATION OF TYPHUS VACCINE POTENCY*

HENRYK MOSING

As compared with bacterial vaccines the evaluation of the efficacy of typhus vaccine is particularly difficult. This is mainly because the cultivation of the typhus rickettsia requires the presence of living tissue: such as the intestine of the louse, the tunica vaginalis of the guinea pig or rat, the lung tissue, the tissue explants in vitro, and finally the developing egg. Under these circumstances the various methods used for the growth of rickettsiae and preparation of the vaccine may affect the intrinsic values of the respective product.

The following are the possible methods of evaluation:

1. *The numerical determination* of rickettsiae in stained preparations. This method although apparently the simplest is not always reliable because the rickettsiae tend to adhere to larger particles in which they cannot be properly stained and differentiated. Furthermore, in the case of the louse vaccine the differentiation of *R. prowazeki* from *R. pediculi* or *R. quintana* may offer difficulties.

2. *The quantitative method* in determining the number of infected lice intestines used for the preparation of the vaccine, the amount of the mouse lung tissue or of the infected chick embryo although based on logical calculation is in practice unreliable because of the variable intensity of infection.

3. *The turbidometric method* is not exact in view of the presence in the vaccine of residual animal tissue. A wide range in the number of rickettsiae was found in comparing vaccines from different laboratories or even of various lots from the same institution.

4. *Titration in guinea pigs* is accepted and in general use since Weigl introduced the D.I.S.—the "*Dosis Immunogena Minima*"—the smallest amount of vaccine which immunizes the majority of test guinea pigs against typhus infection. In

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the case of louse vaccine (prepared from suspensions of 100 lice intestines in 1.0 ml. phenolized saline) serial dilutions containing from 10 intestines to 1/100 of the intestine are made. Each concentration is inoculated into 5 guinea pigs 3 times in increasing doses. Two weeks after the last inoculation all guinea pigs are challenged with typhus. Animals treated with the stronger vaccine show no fever, those inoculated with a weaker vaccine react with slight fever while guinea pigs receiving the smallest amount like the controls show no immunity. The dose of the vaccine which immunizes most of the animals of the tested group (D.I.M.) is then multiplied by 200 (body-weight of man). This relatively accurate method requires a large number of guinea pigs and is costly. Furthermore, absence of fever does not exclude a possible natural resistance of the guinea pig or an inapparent infection. On the other hand, extragenous factors such as a variable room temperature may contribute to fluctuation of the body temperature.

5. *Skin tests.* Fleck in Poland indicated the possibility of evaluating typhus immunity of vaccinated persons in using an extract of *B. proteus X19*, the so-called "exantine" for skin tests, also used by Giroud in Tunisia. Although these skin reactions are specific and of diagnostic value as to susceptibility or resistance to typhus, their application for vaccine evaluation is questionable.

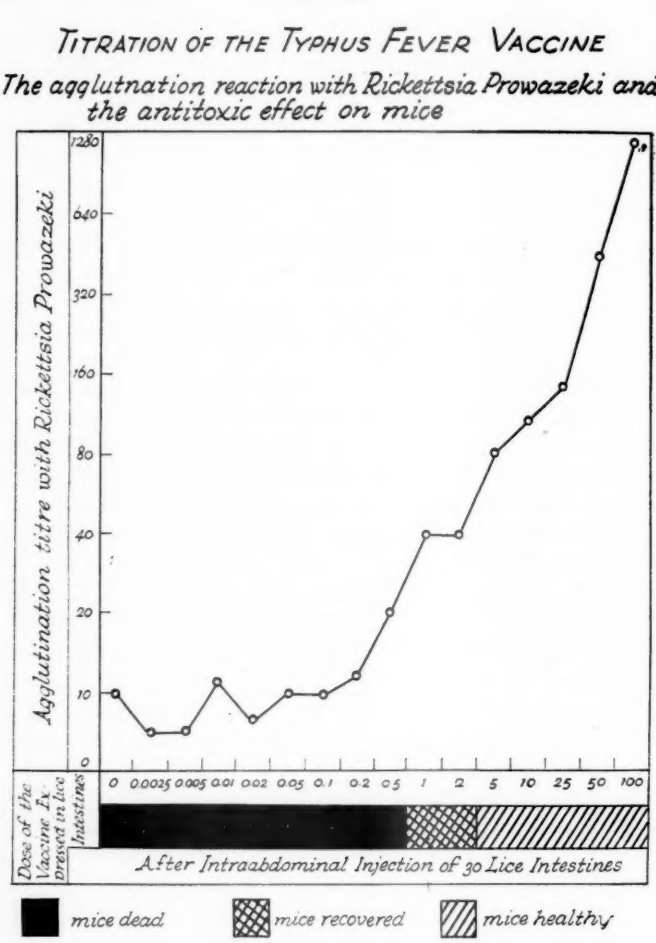
6. *Weigl's reaction.* The microagglutination of rickettsiae although a tedious method offers good results in revealing specific antibodies before the Weil-Felix reaction appears. In a series of observations on persons immunized against typhus it was possible to establish a parallel between the efficacy of the vaccine and the agglutination titre. This was recorded on 7,000 individuals immunized by various methods and tested before and after vaccination. Two types of agglutinins were produced depending on the strength and value of the vaccine: the weaker vaccine induces a gradual waxing of the titre, whereas a rapid rise of agglutinins (titre of 1:200 or higher) follows the first injection of a strong vaccine. It is to be noted that the height of the titre will not be affected by subsequent injections.

In spite of individual differences it is feasible on the basis of the agglutination titres for *R. prowazeki* to evaluate the potency of the vaccine. In this regard it is advisable to consider the titre obtained at the end of the first week following the first or second injections. As a rule all persons or guinea pigs receiving the same lot of typhus vaccine show at this time the same agglutination titres.

7. *The antitoxic effect in mice.* It has been shown by Gildemeister and Haagen (1940) that typhus rickettsiae cultivated in developing eggs or in mouse lung tissue are fatal to mice within 24 hrs. after intra-abdominal injection. This has been corroborated by Bengston, Topping, and Henderson (1945) who use the intravenous route of injection. The fatal effect attributed to toxins produced by the rickettsiae can be prevented by neutralization with serum of convalescents from typhus or by the serum of vaccinated persons. In our experience relatively large numbers of typhus rickettsiae (20 louse intestines) are necessary to kill a mouse. However, vaccinated mice tolerate 50 or even 100 infected intestines. Whatever the nature of the toxic substance may be, it would seem possible to titrate the vaccine by determining the D.I.M. which would protect mice against the otherwise fatal typhus infection.

A comparative study of these methods shows that the guinea pig test, the agglutination of *R. prowazeki*, as well as the mouse protection test can all be correlated in the evaluation of the vaccine. Table I shows a steady increase of agglutinins in mice injected with various doses of vaccine previously tested on guinea pigs beginning with 0.0025, and increasing to 100 lice intestines. All mice were subsequently injected with 30 intestines of heavily infected lice. Control mice or those receiving a low dose of vaccine and showing a titre of 1:40 came down with typhus but survived, whereas mice vaccinated with a larger dose and showing a titre of more than 1:40 remained unaffected.

The results of the present study indicate the superiority of the mouse protection test in the evaluation of the potency of typhus vaccine.



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IMMUNIZATION AGAINST TYPHUS FEVER IN POLAND DURING WORLD WAR II*

RUDOLF WEIGL

The present paper which originated in 1939 has been supplemented by our own observations as well as by the experience of other workers in the field of typhus research. Particular attention was paid in this study to the results of the large scale immunization against typhus with Weigl's louse-vaccine. A total of 5–6 million individuals were vaccinated during German occupation against typhus in the eastern zone of war operations. Of these, one million civilians of the endemic areas in eastern Poland were treated. In order to double the number of vaccinations the vaccine was used in its half strength. Furthermore, due to the wartime working conditions, the quality of the vaccine was below its previous standard. It is estimated that the immunizing value of the vaccine was reduced to 1/3 or 1/4 its previous quality. Instead of the previously used 100 intestines of infected lice their total number for one course of immunization of man was reduced to 25 or 30. In spite of these circumstances the beneficial effect of mass vaccination exceeded all expectations as it contributed to the liquidation of typhus fever on the Eastern front.

In addition to the louse-vaccine, the Cox eggyolk-sac product prepared in Germany and the mouse-lung vaccine supplied by Helen Sparrow were used. The latter product prepared in France, Switzerland, and in small quantities in Lwow, has found a wide application in the Soviet Union.

A comparative experimental study on the efficacy of all three types of typhus vaccine was carried out in this Institute not only on laboratory animals but also on men. As has been repeatedly stated by the author one of the advantages of the louse vaccine is the fact that the human body louse is

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the optimal medium for typhus rickettsiae of all types regardless of origin. It is also known that a 100% and long lasting immunity against typhus can be achieved only when homologous rickettsia strains are used for the vaccine or if the latter is polyvalent. Our experience has shown that it is not always possible to grow every strain of louse-borne typhus recovered from various areas in the developing egg or in lung tissue, at least not in the abundance necessary for vaccine production. In fact, we were able to grow only a small percentage of the isolated strains. It was also found that the mouse lung vaccine from strains of various origin, showed great differences in its protective value. Although relatively good results were achieved with lung vaccines of French and Swiss origin, the latter could not compare with the efficacy of the louse vaccine. Furthermore, the comparison of several lots of the mouse-lung vaccine prepared by uniform methods in this laboratory and containing the same number of rickettsiae also showed wide differences in the immunizing potency, some of the lots being entirely inactive.

These results were not surprising inasmuch as the lung tissue of the mouse is not an appropriate medium for *R. prowazeki*. The analysis of the louse-borne typhus suggests that *R. prowazeki* is from time immemorial maintained in the same unchanged biological system—human louse and man. This led to the rather one-sided and rigid organization of the rickettsia. Owing to its rigidity this rickettsia has lost its adaptability to different exterior ecological factors. When confronted with such unusual medium as the mouse lung the rickettsia in order to survive had to undergo deep changes through the modification of its type and perhaps through a process of mutation. It is therefore logical to conceive that simultaneously a transformation of immunogenic properties of the organism could have taken place. The extent of these changes and whether they have reached their endpoint or are still in a fluid state are difficult to foresee. For these reasons the actual immunizing value of the mouse lung vaccine is a variable and not a fixed entity.

In my own experience evidence is being accumulated for the past eight years that the rickettsia strains of louse-borne

typhus maintained by continued passages in mice are slowly but steadily diverging from their original type, at the same time gradually approaching the murine type. It may be recalled that a vaccine of the murine type of rickettsia will not protect against louse-borne typhus.

In view of the above possibilities and in order to prevent the unpredictable transformations, only those strains were used which after 2–3 mouse passages were subsequently carried in 2–3 transfers through louse and then returned to mouse. The same principle was applied for the cultivation of rickettsiae in developing egg.

As to the American Cox vaccine the question arises as to whether the strains used although of European origin are homologous with the strains responsible for typhus epidemics in Eastern Poland. Should the strains contained in the Cox vaccine be heterologous, a lower protective value can be expected. The degree of the protection can only be evaluated by large scale vaccination in various countries of the European continent.

The typhus egg vaccine was manufactured during the war in Germany by the "Behring Werke." The first series proved either valueless or of little protective value only. However a much higher potency was achieved when the vaccine was manufactured in Lwow under the supervision of Dr. Kobasta who followed my advice and the above considerations. The improvement resulted from the adoption of rigorous biological, serological and histological controls of all the strains used, in addition to the alternate passages from egg culture to louse. Although the experience with the "Behring-Lwow" vaccine was satisfactory it was outranked by the louse-vaccine as far as the degree and duration of immunity are concerned.

SOME CONSIDERATIONS PERTAINING TO ACUTE LEUKEMIA, WITH CASE PRESENTATION

M. FEJGIN*

One of the problems of acute leukemia is the question whether there is only one form of the disease—myeloblastic leukemia—or whether several forms can be distinguished, namely the lymphoblastic, monoblastic, and erythroblastic leukemias. The various opinions in this matter depend not only on different viewpoints on the origin of the blood cells, but in some measure on the difficulty of differentiation of the blood cells. This holds true particularly, for the past, when bone-marrow examination was not in general use in the clinic. The term "lymphatic acute leukemia" for instance, results most certainly from the impossibility of differentiation of the small lymphocytes from the very young bone-marrow elements appearing in the peripheral blood in cases of monocytic leukemia classified by some authors as "monoblastic acute leukemia." However on the ground of bone-marrow studies most hematologists agree with Naegeli that these cells are to be considered as pathological elements, the so-called "promyeloblasts" in acute myeloblastic leukemia or "acute myeloblastosis."

The number of white blood cells in acute leukemia is of less importance as compared with their morphologic character. According to Naegeli the disease begins often with a leukopenia, but later the white cells increase in number. Not infrequently an extreme leukopenia persists to the end—the aleukemic form. The blood picture changes rapidly in such cases; the granulocytes disappear from the circulating blood, whereas numerous typical forms, similar to small lymphocytes with scanty cytoplasm, are present. These cells cannot be distinguished from the actual lymphocytes. Without bone-marrow examination such cases were considered as acute lymphatic leukemias. Naegeli called attention to the absence

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in these cases, of myelocytes, promyelocytes, and true myeloblasts. He called this phenomenon "hiatus leucaemicus," characteristic for acute leukemia, in contrast with the chronic form.

The rapid and stormy evolution of acute leukemia accompanied by the appearance of atypical cells in the blood led some authors to consider acute leukemia as a form of sarcomatosis attacking the hemopoietic system. The bone-marrow changes in acute leukemia usually precede those in the peripheral blood. The bone-marrow is in such cases particularly poor in granulocytes with preponderance of non-differentiated small myeloblasts or "primitive cells" also known as "promyeloblasts" of Naegeli. Not infrequently larger cells of the monocytic type appear with abundant cytoplasm and with amitotic cell divisions. Eosinophilic and basophilic cells are scanty as compared with their increase in chronic leukemia. The spleen and the lymph glands are in most cases not enlarged, though occasionally a palpable spleen and some enlargement of the submaxillary glands can be noted. According to the dominating syndrome, several clinical forms of acute leukemia can be distinguished (Nowodworski): 1. An anemic form—the most frequent, with less stormy and less acute onset, and usually of longer duration, sometimes difficult to differentiate from aplastic anemia. 2. The septic-ulcerous form, with necrotic sore throat, pharyngitis, high septic fever, stormy course and rapid death. 3. Hemorrhagic form, with rapid evolution of a severe hemorrhagic syndrome.

The differentiation of acute leukemia from aplastic anemia is not always easy. The same applies to pernicious anemia and septic lymphatic reactions. The absence of megaloblastosis, bilirubinemia, of the characteristic tongue lesions (Hunter's tongue), and failure of liver therapy permit the exclusion of Biermer's pernicious anemia.

As to the etiology of acute leukemia Heilmeyer and Mallarme consider this disease as a sarcomatosis of the hemopoietic system, while others consider it as a type of sepsis. A filterable virus as causative agent has also been suggested.

It is evident that acute leukemia presents many unsolved problems concerning its etiology, blood, and bone-marrow changes, differential diagnosis and therapy.

Case report: The following case illustrates the difficulties concerned in the differentiation and diagnosis of acute leukemia. It concerns a boy of 18 admitted to the hospital March 6, 1946, with complaints of general weakness, dizziness, sensations of compression in the heart region, and frequent bleeding from the nose. His sickness began in December, 1945. He gave a history of measles, frequent sore throat, and no blood diseases in the family. The patient was pale, with somewhat enlarged submaxillary glands, and a few petechiae on the skin of his extremities, thorax, and oral mucous membranes; lungs and heart without particular changes; abdomen not painful; liver and spleen not palpable; nervous system negative; pulse 78/min.; arterial tension 130/80 mm. of Hg.; temperature normal; urine normal; stool strongly positive for blood; blood Wasserman negative; chest X-ray negative. The blood count on March 7, showed: hemoglobin 40%, RBC 2,200,000, white cells 4,800: polymorphoneuclears, 20.4%; stabs, 2.8%; small lymphocytes 72%; monocytes 2.8%; eosinophiles 2%. Lymphocytes were of normal appearance generally, although smaller than usual, with a very narrow cytoplasm, or without any cytoplasm at all. There were many Reider forms. Red cells were not uniformly stained and showed a marked poikilocytosis with no nucleated forms. Bleeding time was 15.5 (normal 1–3), coagulation time 13–18 (Stephen-Fonio method), clot shrinking time delayed; thrombocytes 40,000; Rumpel-Leede sign strongly positive; bilirubin-serum lever, 1.5 van den Bergh unit. The picture was that of considerable anemia with leucopenia, lymphocytosis, and hemorrhagic diathesis.

If the 72% small monoculears in the patient's blood should be considered as normal lymphocytes, we would have a case of bone-marrow insufficiency similar to Frank's hemorrhagic aleukia. In this case, it is not quite comprehensible why the lymphocytes number as high as 3,456 in 1 cmm. (72% of 4,800). The presence of a great number of irregular cells (naked and Reider's forms), a complete lack of medium size and large lymphocytes, and the similarity of the small lymphocytes to Heilmeyer's "primitive cells" in acute leukemia, raises doubts as to the true nature of the small "lymphocytes" and to the correctness of our first diagnosis of "hemmorhagic aleukia." The next blood analysis, March 3, showed a similar result. It was then decided to perform a sternal puncture with the following bone-marrow count: myeloblasts 15%, promyeloblasts 6%, primitive cells (analogous to the small mononuclears in the blood) 8%, young cells 20%, stabs 5%, polynuclears 5%, eosinophiles 1.25%, megakarrocytes 0. The red cell count relative to 800 white cells, was as follows—microblasts: orthochromatic 10, polychromatic 8; normoblasts: orthochromatic 54, polychromatic 24; macroblasts: orthochromatic 5, polychromatic 6.

The bone-marrow picture was of a leukemic character with white cells in all stages of development from the youngest primitive cells to the mature ones. Into the periphery passed the youngest and mature forms only, producing a "hiatus leucaemicus" as shown by Naegeli in acute leukemia. This led us to the diagnosis of acute leukemia, though the subsequent clinical course was not typical.

During the first 5–6 weeks the values of hemoglobin, red and white blood cells and thrombocytes fell to a low level. On April 2, the blood examination showed HB 20%, RBC 1,060,000; WBC 1,400, with 69% primitive cells. On May 14, the HB was 15%, RBC 620,000; WBC 800, with 84% primitive cells; thrombocytes, 2,300, bleeding time over 30 sec. A stationary period occurred until July when a distinctly clinical remission could be observed though without hemotological improvement. The blood examination on July 31 showed HB 24%. RBC 1,050,000; WBC 1,800, with 68% primitive cells. On August 10, HB was 40%; RBC 1,600,000; WBC 1,600, with 66% primitive cells. No enlarged lymph glands, no palpable liver or spleen were observed. The general condition of the patient in spite of the unsatisfactory laboratory reports, showed a remarkable improvement.

Ulceration of the oral mucous membranes are one of the most constant and characteristic signs of acute leukemia; in our case, they were insignificant and transitory, having been found only at the beginning. The hemorrhagic diathesis, very distinct on admission, especially the obstinate epistaxis, ceased on April 16, although the thrombocyte count was 3,500, and bleeding time over 30 seconds. On June 26, a sternal puncture was again performed with the following result: primitive cells 11%; myeloblasts 3%; promyeloblasts 4.2%; young cells 36%; stabs 6.3%; polymorphonuclears 2.3%.

It is evident that the most dangerous and constant syndromes usually accompanying acute leukemia, namely the septico-ulcerous and the hemorrhagic symptoms, were in our case comparatively slight and transitory, in spite of severe blood and bone-marrow changes. The prognosis is probably unfavorable notwithstanding the momentary clinical improvement.

The treatment consisted of antihemorrhagic remedies ($CaCl_2$, coagulen, klauden), nucleotrat and concentrated liver extract intramuscularly, redoxan, 500 mg. intravenously, and frequent blood transfusions of 300 ml. The patient received 10 transfusions in 5 months. They influenced his condition

favorably, stopped nosebleed, and produced healing of mucous membrane ulcerations in the mouth. The high fever at the beginning indicated a possible secondary infection. Penicillin was therefore administered, 200,000 to 250,000 units daily, totaling 5,000,000 units. This treatment had undoubtedly the effect of stopping the development of sepsis.

Summary and Conclusions

(1) The hemorrhagic syndrome in acute leukemia does not necessarily correspond to the laboratory findings (thrombocytes and bleeding time). The former depends on the condition of the blood vessels, while the latter can be influenced favorably by liver extract, frequent blood transfusions, massive doses of vitamin C, etc.

(2) The septic-ulcerous syndrome in acute leukemia is a secondary phenomenon. It results from the attenuation of patient's resistance consequent to the profound bone-marrow and blood changes. This condition can be controlled, at least temporarily, by penicillin therapy in sufficiently high doses, supplemented by blood transfusions.

(3) The final issue of acute leukemia cannot be influenced by any of our modern therapeutic measures. Bone-marrow changes continue notwithstanding the clinical improvement of the patient.

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OBSERVATIONS ON THE BENEFICIAL EFFECT OF BLOOD TRANSFUSIONS ON RELAPSES IN BENIGN TERTIAN MALARIA*

HENRY MAKOWER

Malaria was before War II a rare disease in Poland. However, with the migration of troops and repatriation of civilians during 1944–46 numerous cases of acute and chronic malaria were observed. Due to shortage of atabrine and plasmochine whenever quinine was available malaria patients were treated with quinine only, but some of them responded poorly to the drug. Attempts were made to influence the course of the disease by blood transfusions, the results of which are reported herewith.

Case 1. Private P. J., 47, was admitted to the hospital August 18, 1944, with the diagnosis "Dystrophia alimentaris" and suffering from chronic bloody diarrhea. A typical malaria attack was observed September 3rd, a relapse of his previous malaria apparently acquired in Central Asia in 1943. After two days of quinine treatment (2 gm. daily) the fever subsided. Spleen and liver were palpable. Diarrhea with blood and mucus persisted. Blood examination: RBC: 2,870,000, Hb 54%. Patient was treated with 0.5 gm. quinine three times daily. On September 19, a new attack was noted with *P. vivax* in the blood. Irregular fever ranging between 37–39° C. was registered in spite of quinine treatment and on September 30, a typical malaria attack was observed. Since then daily acute attacks were recorded with presence of malaria parasites in the blood. Blood examination on October 6, revealed: RBC: 2,730,000; Hb 60%; WBC 3,000. The condition of the patient was rapidly deteriorating. Quinine was then withdrawn and a blood transfusion of 250 ml. of stored blood was administered, repeating the same procedure two days later. Although the general condition of the patient showed rapid improvement parasites were still present in the blood. In view of signs of pernicious anemia (Hb 70%, RBC: 2,630,000) concentrated liver extract (Pernaemyl) was injected intramuscularly once weekly. Within the next two weeks when malaria parasites reappeared a third blood transfusion was given, this time 500 ml. In addition, daily injections of 0.3 gm. atabrine intravenously for 5 days and plasmochine (0.02 gm.) intramuscularly were

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administered. This combined therapy was well tolerated. On October 27th parasites were still present but three days later the blood became parasite free for the first time. The blood count showed improvement: Hb 70%; RBC 3,300,000; WBC 3,600. The patient was feeling well, his blood was parasite free for a number of weeks. He was discharged from the hospital.

Case 2. Private J. K., 40, admitted to the hospital August 26, 1944, with the diagnosis of malaria. The case history showed malaria and diarrhea since 1943 when the patient was in Central Asia. The present illness dates from May 19th with attacks every third day. Previously quinine treatment had no effect. Spleen was palpable. On August 27th a typical malaria attack occurred. Urinalysis showed increase urobilin and presence of red cells. Malaria attacks continued every third day despite daily intake of quinine (1.5 gm.). On September 6th patient underwent a minor eye operation followed by chill and fever. The temperature remained normal and quinine was discontinued until September 14th when a second similar operation was performed. A new malaria relapse followed the operation and quinine treatment was resumed. During the treatment (2 gm. daily) several relapses occurred and the patient's condition became worse. Blood examination revealed: Hb 54%; RBC 2,430,000; WBC 3,900; anisocytosis and toxic forms of leukocytes, also numerous malaria parasites (P. vivax). Daily severe attacks of fever aggravated the situation. Encouraged by the effect of the blood transfusions in the first case 250 ml. of stored blood were given intravenously. Quinine was resumed but plasmodia were still present. Three days later 500 ml. of blood were given. The blood showed: Hb. 82%; RBC 3,560,000; WBC 5,100; a moderate anisocytosis, few microcytes and normoblasts. Quinine was discontinued and atabrine (0.1 gm. orally 3 times a day) was given. After two days of atabrine treatment temperature became normal, diarrhea disappeared and the patient, steadily improving, was discharged.

Discussion and Summary

Both described cases suffered from chronic malaria complicated by bloody diarrhea and became resistant to quinine treatment. Malaria attacks sometimes mitigated by quinine gained in severity and frequency and were accompanied by anemia of the pernicious type. At this stage blood transfusions were initiated which had a drastic effect on the course of the disease. Temperature became normal, and the general condition was rapidly improved. However, malaria parasites remained in the blood; in other words, the manifest disease was

transformed into a latent form. After administration of atabrine and plasmochine in the first case and atabrine to the second patient, blood was rendered parasite free.

As to the question whether the described cases were quinine resistant or whether quinine was not absorbed properly by the intestinal tract as a result of a long lasting diarrhea could not be solved under the difficult working conditions. The beneficial effect of blood transfusions is probably due to the stimulation of the defense mechanisms, as it is usually admitted.

ATOMIC ENERGY

JAMES B. CONANT*

To cover the subject of atomic energy in one brief talk is both a large order and a delicate operation. In the first place, there are so many aspects of the topic which lead into highly technical matters that a speaker must be on his guard to prevent the exposition from becoming an elementary lecture on nuclear physics. In the second place, it is no easy matter to discuss atomic energy for military purposes—in short, the atomic bomb—without appearing either too complacent on the one hand, or too hysterical on the other.

Ever since the two bombs were dropped on the Japanese cities of Hiroshima and Nagasaki, the public discussion of atomic bombs has veered first to one side and then to the other. Those of us who have lived with the problem for a somewhat longer time than others—and I have been living with it off and on since the summer of 1941—are in a bit of a quandary when we are asked to speak on the subject in public. Clearly we have a duty to impress on everyone the extreme gravity of the threat to Western civilization inherent in the atomic bomb, and at the same time we do not want to produce hysterical reactions by dwelling too exclusively on the devastating effects of an atomic war.

I often think that there is a close analogy between this dilemma and that which a doctor faced in the days before insulin was discovered. As some of you may know, in those days a man with diabetes could live a fairly active life provided he was extremely careful with his diet. The physician, therefore, had to frighten the patient sufficiently in order to make him obey the dietary rules; but if he frightened him too much, despondency might set in—hysteria if you will—and the patient might overindulge in carbohydrates in a mood of despair, with probably fatal consequences.

Following out this analogy, I suggest that what we must do in the United States is to face up with boldness and vision to

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*President of Harvard University. Delivered February 21, 1947.

the realities of the situation in regard to atomic energy. We must neither seek comfort in wishful thinking nor compensation in flights of hysterical fantasy. We must recognize that we have a grim problem on our hands and seek to solve that problem with all the courage and understanding at our command. Then, perhaps, the equivalent of the discovery of insulin will come along—perhaps, no, more than perhaps, almost certainly if the governments of the great nations desire it—an effective control of atomic energy on an international scale will be developed and mankind will be started down a new road toward the abolition of major wars.

It is, therefore, with a spirit of hard-headed idealism that I hope you will bear with me today as I discuss certain phases of the topic of atomic energy. To some degree you are familiar with the basic facts about nuclear energy and the progress of the international discussions to develop a system of international control. It is my purpose to summarize the present situation as presented to the public by a report of the United Nations Atomic Energy Commission. This report, dated December 31, 1946, is a public document but has received all too little attention in the press. It speaks with the authority of ten nations, and while only a progress report, it is to me an omen of good cheer for it points the way which the world must take eventually if we are to avoid an atomic war.

But before I discuss this document which is directed largely to the future, I should like to call your attention to that extraordinarily interesting article by Mr. Stimson in the current issue of *Harper's Magazine*. This article deals with the past and clears up, I hope, a certain confusion in the public mind. The Decision to Use the Atomic Bomb (and that is the title of the article), the former Secretary of War points out was only taken by the President after the most careful and searching appraisal of the then military situation. In recommending the use of the bomb against two Japanese cities, Mr. Stimson had in the forefront of his mind the fact that a full-scale invasion of Japan was scheduled on November 1, 1945. And he argues with great force that if fighting had actually occurred on the Japanese Islands, considerations of military prestige

would have made a surrender of the type which was achieved impossible. President Compton of M.I.T. has an interesting article on this point in the *Atlantic* for December, by the way.

What many of the critics of the decision to use the bomb without prior specific warning or public demonstration have never known until Mr. Stimson's article appeared was that we had only two bombs ready in August, 1945, and "our rate of production at that time was very small," to quote Mr. Stimson's own words. We had a new weapon never tried on the battlefield, only one atomic explosion had ever been seen—the test in New Mexico a few weeks before. No one could guarantee that those two bombs would work. To quote Mr. Stimson again, "Nothing would have been more damaging to our effort to obtain surrender than a warning or demonstration followed by a dud—and this was a real possibility. We had no bombs to waste. It was vital that a sufficient effect be quickly obtained with the few we had."

As to the devastation of Hiroshima and Nagasaki, it was of the same order of magnitude as that produced by the great fire bomb raids on Tokyo. The difference, and the all important difference, is that it required many hundreds of planes to carry the fire bombs; it took just one plane to carry the atomic bomb. In that comparison lies the significance, the dread significance of the atomic bomb. Destruction of civilian targets, widespread death and suffering to civilians became part and parcel of the last war long before the atomic bomb was introduced. If there is another major war it will be the accepted pattern.

The discussion of whether or not the United States should have used the bomb has been a necessary, even a healthy discussion, to my mind. We are a nation of idealists. We are a nation committed to the ideas of peace. The brutal facts of war are extremely distasteful to us. If no voices had been raised in protest against the use of the bomb, this would not have been the America our youth was fighting to defend. Yet the dissenters, to my mind, have been mistaken; in part because they failed to understand the nature that modern war had assumed before the atomic bomb was used, in part because they confused the existence of the bomb with the use

of the bomb—(if Mr. Stimson's recommendations to the President had been negative, we should still have the problem of the bomb right with us) but largely because some of the basic facts are only now available. From here out any further discussion can proceed on sounder ground.

Now, may I revert to a statement I made a moment ago: if it had been decided *not* to use the atomic bomb in the Japanese war, the problem of the atomic bomb would still be with us. I should like to correct this statement for it would be more accurate to say that the problem would be with us and in a much more confused and ambiguous state than it is today. We have had confusion enough, heaven knows, about the national and international control of atomic energy, but imagine the situation if the bomb had not been completed in time to end the Japanese war. Leaving aside all question of the casualties on both sides, the desperate land fighting and the devastation, just imagine the strange international situation which would have resulted if we had been ready with the New Mexico test just as Japan had been finally conquered by what we now call orthodox means. Those of us who were in on the secret and had thought about it a long time would have been as disturbed about the international control of this revolutionary weapon as we are now, but would anybody else? Would even the harrassed officers of the government? We have had a great deal of debate about secrecy in the last eighteen months, but what a hauling and pulling there would have been had the bomb never been exploded in battle. We have had some skeptics express doubts as to whether it is indeed a revolutionary weapon, but what skepticism there would have been if there had been no actual use in war!

As I shall say later, I am an optimist about the chances for eventually working out a scheme for international control of atomic energy—a scheme for removing this weapon from the armory of all powers, a scheme which by its very nature would be a long step toward lasting peace. But if the weapon had been perfected just as the war was closing, or shortly thereafter, I must admit I think it would have been well nigh impossible to work out any method for control by an international agency.

Such a very "if-ly" discussion of what might have been is perhaps not entirely out of order in attempting to right our perspective about this matter of "good fortune" or "bad fortune" concerning the discovery of how to release atomic energy. To my mind we have been all too slow to count our blessings in this matter. Granted that it would have been a matter for rejoicing if the laws of nature had been such that an atomic bomb were impossible, but the realm of physics being what it is, in fact, then clearly it was only a matter of time before the potentialities of the atomic bomb would have been discovered. To my mind, it is very clear that the democracies were most fortunate in the timing—a year earlier for the completion of the first two weapons would have been much better, of course. But three years earlier for the basic discovery of atomic fission (made in 1939) and the Germans certainly would have developed the weapon in time to conquer the entire world. What that would have meant I leave to your imagination. A few years later for the completion of the American effort and the potentialities of the bomb would have existed, but without public knowledge. The resulting confusion I have already called to your attention. So, leaving out of account entirely the effect of the bomb on the Japanese war, I say the timing was very fortunate, indeed. I call your attention to these calculations for in these days of gloom and pessimism we do well to count our good fortune when we can.

So much for the past. Now let me turn toward the future. Let me consider, if I may, what the prospects are for the international control of atomic energy and the application of this energy for civilian purposes. In attempting to gaze into the crystal ball, I shall be guided by the report I referred to at the outset, namely, the "First Report of the Atomic Energy Commission to the Security Council of the United Nations" dated December 31, 1946. My factual information will be drawn from this document.

Before considering the question of international control a word or two about the prospects for the use of atomic energy for industrial purposes are in order. For the objective of any scheme for international control is clearly twofold. On the one hand, the world wants to remove the threat of this new

weapon; on the other, we desire to have atomic energy available for peaceful purposes.

I am sure you are all familiar with the basic facts about nuclear energy which have been set forth many times in the last eighteen months. But just as a summary I should like to quote from the report I have mentioned. The technical subcommittee of the United Nations Commission uses these words in a summary of one of its chapters:

"Atomic energy in amounts of importance for industrial activities is obtainable only from nuclear chain reactions which like fire are self propagating. Three materials are known which are useful as nuclear fuels for a self-sustaining chain reaction: only one of these occurs in nature, Uranium 235, constituting 0.7 per cent of Uranium; the other two, Plutonium and Uranium 233, can be produced by nuclear reactions from Uranium and Thorium, respectively. Nuclear fuels may be 'burned' at a controlled rate in a reactor, or in a runaway explosion as in a bomb. The raw materials for atomic energy, Uranium and Thorium, occur in widely scattered ore deposits."

There in a nutshell you have the basic data. Now what about the prospects that these nuclear fuels can be used for the production of industrial power? Here is what the report has to say on that subject: "The large scale production of electric power from atomic energy appears feasible though still in the developmental stage." In short, the authors of this report do not care to run the risks of prophecy by saying when and at what cost. They are wise men and I shall follow their example. After all, we are just at the beginning of a whole new chapter in physics and we must be patient. It is in the very nature of research and development that no one can in advance lay down an accurate time-scale. It is in the nature of scientific and technical work that one is always going around the unexpected corner. Therefore, beyond saying that large-scale production of electric power from atomic energy appears feasible some day, I think one should be very careful in his speculations.

But when the experts say this much, it means a great deal, of course. In terms of the next fifty years it makes little difference whether what now appears feasible is reduced to practice in 1950 or 1970, let us say. What it amounts to is

that we are told that here is a promising development of a new source of energy for peaceful purposes. Unfortunately, as we all know, the same nuclear fuels on which this peaceful development must be based are the same fuels for the construction of an atomic bomb. Therefore, "There is an intimate relation between the activities required for peaceful purposes and those leading to the production of atomic weapons; most of the stages which are needed for the former are also needed for the latter." Unless we are prepared to forego all the possible advantages of the use of nuclear fuels by shutting down all the mines of Uranium and Thorium by international law and keeping them shut, we have either to face a future where atomic bombs are part of the armament of each major nation or we must arrange for an international authority to control the production and uses of these fuels.

Now the first is no real alternative. To shut down the mines and be sure they were all kept closed by international inspection would be as hard as setting up an international control of the production. Furthermore, these materials are often by-products of the mining of other metals. This clearly complicates the situation. I cannot imagine that any country would be willing to forego research and development in a field which *may* (and I underline the may) mean so much for an industrial civilization. Finally, though the atomic bomb is a terrible menace to industrialized nations as a weapon of war, the international control of nuclear fuels holds great promise as a road to a lasting peace.

For all these reasons, I think we may assume that the mining of Uranium and Thorium will continue and research and development on nuclear fuels and their application will proceed in all industrialized nations. This assumption brings us directly to the need for international action. I say directly for I take for granted that all of you have already heard enough about the destruction of the atomic bomb and its peculiar and special characteristics as a weapon of surprise to be ready to say we must eliminate it if we can. It is certainly not just one more weapon; it is a unique weapon, perhaps the absolute weapon as some military strategists have claimed.

What has been proposed by the United Nations Commission is essentially the United States plan. An international or, one might say, a supranational atomic energy authority would be created by a treaty or convention in which all of the nations, members of the United Nations, should be entitled to participate on fair and equitable terms. This international control agency would have the ultimate power over the production and distribution of nuclear fuels. After the scheme was well launched, the manufacture or possession of atomic bombs by any nation would cease; existing stocks of nuclear fuels would be allocated entirely for civilian uses.

I am sure you will all agree that if the major nations of the world can actually agree to all the details required in such a treaty and set up an international authority with such wide powers, we shall be a long way down the road to permanent peace. For if this weapon can be controlled, there should be little difficulty with other items of heavy armaments. But most important of all, if an international agency with such highly important duties can function smoothly for a few years, a pattern will be established that will almost certainly guarantee a long-continued peaceful collaboration among the major powers.

But what are the assurances that such a scheme will work? Can the control of the agency be effective? How will the peoples of the world be certain that some nation is not in secret manufacturing atomic bombs? Here the experts of the ten nations may be listened to with special consideration. They find that technically adequate safeguards can be established provided the international control agency is given sufficient power, including wide power of inspection over mines and potential mines, control of the plants for producing the nuclear fuels, and power of inspection over the industrial plants using such fuels. In short, it can be done if the governments of the nations want it to be done. This is a highly important conclusion from a group of scientists and statesmen of many nations. It gives us hope for the future.

Yet, the pessimists among you may well say that what is technically feasible may not be politically feasible, and shake your heads. No one can say what is politically feasible, of

course. One can only hope and try and above all—be patient. Perhaps because temperamentally I am an optimist, I believe the present negotiations based on the report I have referred to so often will eventually succeed. I make no prophecy as to the time. These negotiations will include not only the drafting of a very intricate treaty to set up the international control agency, but will have to have special provisions about the disposal of the United States' special assets—our know-how, our plants, our stock of nuclear fuels which we presumably have, since it has been officially stated that we are still making atomic bombs. I believe that an acceptable arrangement can be worked out in such negotiations by which, during the transition period, the United States does not run the risk of becoming unilaterally disarmed only to find that the international control scheme is in fact a myth. Certainly acute statesmen, if given the green light by their governments, can formulate a series of stages for putting the international control in operation that will safeguard not only the United States but the entire world.

As to these assets of ours, we must remember that while they are very great today, their value is diminishing. They are like a cake of ice in an open field on a hot sunny day. Everyone agrees to that; but no one agrees how large the cake is or how hot the day may be! But this much is almost certain: some day within the next fifty years other major industrial nations will have a know-how, a plant and stocks of nuclear fuels. Whether their assets in atomic energy will be as up-to-date or as big as ours is beside the point. If we fail to get international control of atomic energy, the time will come when another nation has sufficient nuclear fuel and know-how about bombs to constitute a military threat *by this means* to the United States. When this day arrives, if it ever does, we shall be living in a very unhappy world. War would be a matter of long-range bombardment by both sides and of short duration. Industrial areas and centers of civilian population would probably be the victims of a "superblitz." Whoever was the victor, civilization would be the loser. It is to avoid living in an age of the superblitz with all its fears and

woes that the representatives in the United Nations are now wrestling with this problem of the control of atomic energy.

For the time being there appears to be little that we citizens in the United States can do to forward the work of the United Nations in this regard. When an agreement is reached and the treaty comes before the Senate for ratification, then if there be any who think this is the wrong road, these people will need convincing. But for the present there is no matter for debate. There is need, perhaps, for a thorough realization by all thinking inhabitants of this country of the nature of the problem. As I indicated at the outset, we have to set a course between complacency or indifference on the one hand and hysteria on the other. We need to accept the release of atomic energy as a fact, we need to view the future of nuclear fuels with as much wisdom and as little emotion as possible. We need to pass mature judgment on all proposals and all irresponsible predictions and idle talk. In short, we must learn to live with this latest turn of scientific discovery and development.

May I conclude this address by a word or two of a very personal nature about my own experience? As I watched the secret development of the atomic bomb during the four years of war and at the same time knew of the work of the Medical Committee with penicillin and DDT and blood plasma which promised so much for future health, I often thought of Emerson's famous essay on the Law of Compensation.

In the early days of the work on atomic energy there was a possibility that the constants of nature would be such that atomic energy for power would be possible, but an atomic explosive impossible. That the rate of burning of the nuclear fuels would not be fast enough to give an effective military weapon. We all hoped this would be the case, though the probabilities were slight. In fact, I often thought in that uncertain period that this would be too good to be true—the universe just isn't built that way. So it turned out in fact. Science and its applications have given us marvelous drugs and ways of health, communications, transportation, luxuries of every sort; it has also given us the atomic bomb, the discovery of which was inevitable in a scientific age—only the timing

was uncertain. And about our good fortune as to the timing, I have already expressed my views.

Perhaps, even at the risk of seeming provincial, as a New Englander may I quote Emerson on compensation:

". . . Every excess causes a defect; every defect an excess. With every influx of light comes new danger. . . . There is a crack in everything God has made. It would seem there is always this vindictive circumstance stealing in at unawares . . . this backstroke, this kick of the gun, certifying that the law is fatal; that in nature nothing can be given, all things are sold."

If, following Emerson, we think of the potential power of destruction of the atomic bomb as the price we pay for health and comfort in this scientific age, we can perhaps more coolly face the task of making the best of an inevitable bargain, however hard.

The United States has put forward a reasonable plan for the international control of the new weapon. For the present we must wait with patience while the reasonable proposals for the control of this energy of the United States are explored by the United Nations. When we despair of the delay we would do well to remember that a new international order, like Rome, is not built in a day. And that dismal as will be the outlook if these negotiations fail, if they succeed we may well be launched on a new era of peace for all mankind. Remembering that Emerson warned that "the doctrine of compensation is not the doctrine of indifferency" we can start walking boldly along the tightrope of the atomic age.

NOTE: Following this address, President Conant spoke informally to the students of The University of Texas Medical Branch on the growing relations of chemistry and medicine. He advocated closer relations between pre-medical and medical training.

THE ORGANIZATION AND FUNCTION OF A TUMOR CLINIC

J. Louis Neff*

The concept of the tumor clinic is one which must be credited to the American Society for the Control of Cancer, now known as the American Cancer Society, which in 1930 started a program in coöperation with the American College of Surgeons. This program had for its basic philosophy the idea that the cancer patient would benefit by, and was entitled to, the same type of concentrated skill and effort as was made possible by the establishment in general hospitals of separate services or departments of surgery, obstetrics, urology, dermatology or pediatrics. Since the original program of 1930, the idea of specialized cancer services has resulted in the development of three distinct types of tumor clinics: the diagnostic clinic, the treatment clinic, and the detection center. It is the purpose of this paper to consider each of these services separately and to discuss their respective functions in the total, overall program of cancer control.

Cancer Diagnostic Clinics

Perhaps the greatest single step forward which could be taken in the solution of the cancer problem would be the universal recognition of the fact that cancer is not a single, clearly delineated disease entity, but is rather a generic name for a very complex group or family of individual and individually complicated diseases. Since cancer arises in practically any or all parts of the body and presents—in its early stages at least—vague, obscure and sometimes apparently irrelevant symptoms, its diagnosis calls for the services and skills of practically every one of the specialties or divisions of medicine. It is this complex and obscure nature of the disease which renders it singularly suited to the technique of group thinking, group discussion and group effort. This is the essence of the cancer diagnostic clinic.

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Minimum Standard for Cancer Clinics

The essential elements of the cancer clinic as set up by the American College of Surgeons are:

1. Organization. There shall be a definite organization of the service, and it shall include an executive officer and representatives of all the departments of the hospital concerned in the diagnosis and treatment of cancer. The services of a secretary and of a social service worker shall be available for the purposes of the clinic.

2. Conferences. As an essential feature of the service there shall be regular conferences or consultations at which the diagnosis and treatment of the individual cases are discussed by all members of the clinic who are concerned with the case.

3. Patients. Reference to the cancer clinic of all patients in whom the diagnosis or treatment of cancer is to be considered shall be either voluntary or obligatory in accordance with the vote of the medical staff or of the governing board of the hospital.

4. Equipment. In addition to the diagnostic and therapeutic surgical equipment which is required in every approved general hospital there shall be available an apparatus for X-ray therapy of an effectiveness which is generally agreed upon as adequate, and an amount of radium sufficient to insure effective treatment.

5. Records. In addition to the records which are required in every approved general hospital, there shall be additional records of: (a) Details of the history and of the examination for cancer in different regions of the body, such as are indicated on the form records which are recommended by the Cancer Committee, American College of Surgeons; (b) Details of the treatment by radium or X-ray as indicated on the form records which are recommended by the Cancer Committee, American College of Surgeons; (c) Periodic examinations at intervals for a period of at least five years.

6. Treatment. The treatment of cancer patients shall be entrusted to the members of the staff of the cancer clinic except in cases in which adequate treatment in accordance with the collective recommendation of the staff of the cancer clinic can be procured otherwise

In considering the role of the tumor clinic in the general hospital, it would seem that ideally there should be an arrangement for the compulsory referral to the tumor service of all "ward," "service" or "charity" patients presenting evidence

of neoplastic disease, and the voluntary referral of private patients. As the clinic group grows in stature and in consequent recognition, it might reasonably be expected that this latter group would increase in numbers.

Cancer Treatment Clinics

Although the American College of Surgeons' standards for treatment clinics are the same as those for diagnostic clinics, the philosophies of the two types of clinics are in many respects quite different Many hospitals which are willing to set up a tumor clinic for diagnostic services seem reluctant to extend this group thinking, group effort and group strength into the field of therapy There will be appointed to the tumor clinic staff the chief or some other representative of each of the appropriate special services of the hospital—surgery, urology, gynecology, otorhinolaryngology, radiology, orthopedics, internal medicine, etc. These men will meet together, harmoniously, for the purpose of giving to the cancer patient the benefit of their group thinking and group effort in examination, history-taking and diagnosis—and then refer the patient over to one of the narrow fields of specialization for the ultimate treatment. This seems to be regrettable. If group action is of value in diagnosis, it should be of equal value in the treatment of a disease where the use of surgery might alternate with that of radium or X-ray, or where, as so frequently happens, these treatments must be used in combination, or a disease where a given patient might require the services of several specialists in addition to his surgeon, his radiologist, and his pathologist.

Let it be recognized that cancer therapy, if it is to be effective, is radical therapy. Radical therapy requires courage and self-assurance in large doses, in addition to highly developed technical skill. Each of these qualifications is best derived from constant, repetitive practice. How better can this opportunity for practice be developed than by the segregation of the cancer patient into a separate service of the hospital in exactly the same fashion as we now segregate the patient—or at least the responsibility for the treatment of the patient—

into separate services or departments of obstetrics, pediatrics, ear, nose and throat, and so forth?

The comments of a nationally known pathologist might be of interest in this connection. This man had become attached to a public general hospital in which the tumor clinic was recognized as the tumor service of the hospital, and as such had all the perquisites and responsibilities of any of the other services, including official representation on the medical board. After a few years of association with this service which included an active role in the weekly teaching conferences which were presented by the service to the physicians and dentists of the community, this physician said: "I shall never be able to repay my debt to that tumor clinic, nor to evaluate the good it has done me. For the first time in all my experience as a pathologist I find myself thinking of cancer as something beyond the gross specimen sent down to me from the operating room, or the section presented to me by the technician for microscopic study. I now see the patient as an individual, suffering from many obscure and complicated ailments and afflictions. I want to visit him in the wards. I want to follow him into the operating room. I find myself in closer contact than before with the surgeon and the clinician. I am certain that I am a better pathologist, and I feel confident that I am of greater value to the cancer patient."

Another factor which justifies the establishment of the tumor clinic as a separate service of the hospital, is the question of follow-up. To be sure, the obstetrical service wants a follow-up on its patients—a six-weeks post-partum examination, perhaps even a six months return visit. But there they stop so far as follow-up needs are concerned. Similarly the orthopedic service will be interested in observing the end-results of their surgery and in assuring their patients of good functional results by a limited period of observation and perhaps of physical therapy. To a lesser extent some of the other services might enjoy or even demand a limited follow-up organization. But a cancer patient is *never* discharged from a properly organized and efficiently operated tumor clinic. Frequent observation for the rest of that patient's life is the only assurance against disaster from local recurrence or from

delayed evidence of metastasis. Only by the grouping of cancer patients as the responsibility of a single service can this prolonged observation of the patient be achieved in a practical and workable fashion. Such grouping of patients, even in a hospital of a hundred beds, justifies the employment of the skilled, professionally trained social worker who best can conduct the follow-up service which is one of the prerequisites for approval of a clinic by the American College of Surgeons.

Detection Center

The detection center is the newest of the specialized cancer services which have been developed coöperatively by the American Cancer Society and the American College of Surgeons. Its role is quite different from, but equally important as those of the two previously described.

Let us remind ourselves that the curability of cancer, in general, is in inverse proportion to the extent of the lesion when first discovered. Let us also remember that many types of cancer can be detected either by careful physical examination or by equally careful history-taking before they have progressed to the point where they provide the patient with subjective symptoms which suggest a visit to the physician. Finally, let us look back upon the laudable, but for the most part fruitless, efforts of the organized medical profession to promote the idea of the periodic physical examination. For some reason or other the idea of "Go to your doctor for a health examination on your birthday" never received popular acceptance, but it is a proven fact that "Get yourself examined to make sure you do not have cancer" is causing patients to seek medical advice in what in some cases has proven to be embarrassing numbers, numbers which tax the existing clinic facilities and put a difficult strain upon the available time of the private practitioners. MacFarlane in Philadelphia, L'Esperance in New York, and Webster in Chicago have proven dramatically that an aroused public will accept the idea of periodic medical examination with a specific objective in mind, where they coldly ignore the plea for a health examination when couched in more general terms or on more abstract grounds.

True it is, that the general practitioners of medicine, the so-called family physicians, are perfectly competent to make the type of examination and to take the type of history which are necessary to detect symptomless cancer, but for some reason or another, people seem reluctant in many instances to seek these services from their customary and logical sources of medical care. Perhaps they are fearful of ridicule over seeking an examination in the absence of any tangible need for one; perhaps they have made the mistake of seeking such an examination—a procedure requiring a good forty minutes of time—in the middle of a busy office hour session of their physician and have never been told of the necessity for prior appointment for such special services. Perhaps there is, in some instances, a certain amount of truth in the accusation so frequently made that "my physician is too busy to bother with such things and has to save his time for sick people," or "I went to my doctor and he just laughed at me and told me to forget such nonsense." But in any event, wherever local medical groups have established detection centers, the problem from the very start has been to keep the attendance down to workable numbers and the waiting list short enough to be consistent with the basic philosophy of cancer control measures.

Briefly, the detection center is merely a group service for the purpose of providing to the apparently well person a reasonably complete physical examination backed by a similarly complete history taking. Special attention, of course, is given to those areas of the body where cancer most frequently occurs, including the regional lymph nodes. When properly conducted, patients with stated symptoms are immediately excluded and referred over to their logical source of diagnostic or treatment service. Nothing is done to or for the patient beyond determining whether there are any indications for further diagnostic effort. In the event of suspicious findings, a report is made to the patient's physician of record, perhaps accompanied by specific recommendation—to the physician, not to the patient. Nothing of a diagnostic nature is attempted, *not even a biopsy,* and nothing is told the patient except "we have been unable to discover any evidence of trouble, but

we urge you to come back again in six months and in the meantime to familiarize yourself with the danger signals of cancer and report to your physician at once if one of them should develop," or, in the case of those with suspicion conditions: "We have discovered something of a suspicious nature in your pelvis. We urge you to report to your physician at once for a more complete examination. We will write to him and describe what we have found." This is the full extent of the message given the patient even in the presence of the most conclusive clinical findings.

As the educational activities of the American Cancer Society and of the official health agencies become more extensive and more effective, we may expect that more and more people will be reporting to our tumor clinics with obscure symptoms which upon investigation are found not to be caused by cancer. Perhaps, in fact, one measure of the effectiveness of our attempts to secure early examination of obscure conditions will be the increase in the percentage of patients who are in fact suffering from benign conditions, since the earlier the cancer, the more readily it is confused with something else. For this reason, some way must be found to protect the tumor clinic from becoming clogged with "negative" cases so that the services of the limited group of physicians and surgeons with highly developed cancer skill and experience might be reserved for those patients actually suffering from malignant disease. Perhaps the detection center provides a means for "presorting" patients which will help accomplish this end.

For this reason, and also because the detection centers should be set up primarily as teaching devices both for the public and the professions, designed to teach the importance of periodic physical examination, the staff of such centers need not be, and perhaps should not be, composed of the "specialist" or "consulting" group. True enough the work should be in charge of and be supervised by those of special cancer skill, but the examinations themselves can well be entrusted to the general practitioners.

It would seem that an active and well-run detection center should be made a part of every medical school. If the senior students are assigned to act as clerks or assistants they might

be expected to absorb two important things: first, a concept of the importance of the systematic, complete, physical examination in the detection of incipient disease, and second, the habit of demanding a complete and adequate explanation for any observed departure from the normal, based upon the never-forgotten thought that "it might be cancer."

So much for the immediate and more obvious objective: service to the cancer patient and the potential cancer patient. Do these several types of service have any other function?

Let us cast our thoughts back over the past twenty years of the history of medicine. Much has happened, of course, in many fields: chemotherapeutic agents, the biologicals, the antibiotics, have solved many problems; new chapters have been written in surgery, notably in the fields of plastic repair and orthopedics; new anesthetics have made possible many other surgical advances. Much has happened. But where else in all of medicine and surgery have we seen such dramatic advances as in the field of cancer control? Whether we consider the improvements in diagnosis, in surgery, in radiation therapy, in fundamental knowledge, in popular acceptance and popular support—from whatever angle you view the subject, you meet constantly the one word: "new." It has been said that the bulk of what we know about cancer has been learned in the past twenty years, with a high percentage of that coming in the past ten.

If we accept this statement, it naturally follows that we must accept the statement that nowhere in the fields of medicine and surgery is there such need for educational opportunities open to the professions as exist in the field of cancer control. This education must be of three types: first, fundamental education of the coming generation of physicians, today's medical students. With the constantly increasing element of hope in the cancer picture, the medical school is indeed justified in placing greater emphasis on the subject in its undergraduate curriculum. Is it too much to hope that eventually there might exist in every medical school a coordination of cancer teaching through a duly constituted Department of Oncology?

The second type of educational opportunity is that for the present practitioner to whom cancer is only one of the many problems of an active practice. He needs to be brought up to date; his interest needs to be attracted and stimulated; he needs to be made aware of the cancer problem, of the facilities available for the diagnosis and treatment of the disease, and of the new need for his alertness and diagnostic skill in the face of the anomalous situation of a constantly increasing death rate in spite of a constantly increasing reason for optimism for the individual patient and the specific case. Finally, there is need for the postgraduate training of that group of physicians who desire to make cancer their special interest and its management their special activity.

Where else could we find better machinery for these three types of professional education than could be created by the proper utilization of the opportunities afforded by the detection center, the diagnostic clinic and the treatment clinic or tumor service? It is the announced hope of the American Cancer Society that there shall be made available to every resident of the State of Texas the services of a conveniently located information and detection center; that in the not too distant future there shall be at least one American College of Surgeons-approved diagnostic clinic in each of the fifteen councilor districts of the state medical association; and that additional treatment facilities be developed as rapidly as professional personnel and physical resources become available.

Now may we announce one other hope which probably is fully as important as the other? This is the hope that as these facilities are established they will coördinate their activities with one another and with the activities of the state cancer hospital, not merely for the purpose of improving their techniques, not merely for pooling their statistics for research purposes, desirable as such activities would be, but also for the purpose of creating out of these service facilities a statewide network of cancer teaching centers which would make available for every physician in the state the opportunity to engage in postgraduate study in this important field.

The most recent directory of The American College of Surgeons lists for the State of Texas a mere eight approved cancer

clinics, whether diagnostic or treatment; there is functioning in the state at the present time only one detection center; there is only one place in the state operating on a full-time schedule, where one may go for authentic information and advice. The constructive leadership of the medical profession and the financial support of the American Cancer Society made possible by the generosity of the people of the state are already changing this picture. Let us hope that in the next Approval Number of the Bulletin of the American College of Surgeons this pitifully inadequate list of approved facilities will be greatly expanded, and that in the not too distant future the medical schools, the medical societies, the general hospitals, the departments of health, the State Cancer Hospital, and the American Cancer Society can by their united and coördinated efforts give to the people of the state a system of cancer control activities and facilities which will be second to none in the entire United States.

REVIEW OF THE LITERATURE AND REPORT OF A CASE OF RABIES*

J. M. Barnhart

Definition: Rabies is an acute specific, infectious disease which may affect any warm blooded animal. It has a reservoir in certain of the lower animals, most commonly canines, and is transmitted by biting and salivary contamination of an open wound. Rabies is caused by a filterable, neurotropic virus occurring in the salivary glands and in certain nervous tissues. It causes a disease characterized by destructive changes in the motor nerve cells of the nuclei and cord resulting in a rapid clinical course of excitement, convulsion, paralysis, and death.

Geographical Distribution: Rabies is or has been found in every part of the world except Australia, New Zealand, and Hawaii. It is more or less common in Belgium, France, Italy, Russia, India, Japan, and China; whereas Switzerland, Denmark, Sweden, and Norway have been free of rabies for more than fifty years. The English had almost completely wiped out the disease by 1918 through rigid vaccination, muzzling, high dog licenses, and inflexible quarantine regulations. Their last animal case was in 1923 when a dog was smuggled in by a returning soldier.

On the other hand, the disease is endemic in North America where we can expect approximately one hundred cases a year. Sporadic outbursts occur in various parts of the country, but in general it can be said that Texas and California have furnished the largest number of rabid animals, Texas and Tennessee the majority of human cases.

Transmission: Rabies is primarily a disease of carnivorous animals, 90 per cent of human cases originating in dogs. Wolves, foxes, jackals, coyotes, cats, skinks, cows, and horses are occasional sources. The incubation period in rats is fortunately so short and the virulence is so great that it is difficult for a reservoir to be established. Vampire bats have been definitely indicted in outbreaks on Trinidad. There is only

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one reported case in which it seems certain that the infection was transmitted from person to person. This is remarkable when we think of the numbers of potentially saliva infected individuals who have cared for rabies sufferers. Of interest are the analytical reviews by McKindrich on reports from the Pasteur Institute of 1,007 bites by rabid humans without a single recorded death.

About 16 per cent of bites by rabid dogs will result in human rabies in the absence of preventative measures. The individual case will vary, depending on:

1. The number and severity of the bites. This may account for the almost 100 per cent infection in bites from rabid wolves.
2. Whether the bite was through clothing or hair or was on unprotected skin. This mechanical cleansing of saliva from the tooth is said to lower infectivity by 1:9.
3. The animal inflicting the bite. Incidence decreases in order of wolf, cat, dog, with ruminants far down at the foot of the list. A report from Russian antirabic stations gives a series of 3,522 bites by suspected cows without a death. California reports, however, a single death from a cow's bite.
4. The age. Children are notably more susceptible than adults.

Other modes of transmission than by bites are possible. Laboratory workers have been infected by handling infected tissues. Experiments by many different workers—the latest by Sulkin and Harford—have proven the presence of the virus in the saliva of the rabid animal. Remlinger was able to produce rabies in four out of five attempts by instillation of virulent saliva onto the uninjured nasal mucosa of guinea pigs.

The virus has been shown to appear in the saliva five to eight days before symptoms begin and is present up to the time of death. It is therefore possible for a dog to seem perfectly well at the time of infection and for several days following. However, an individual bitten up to fourteen days before symptoms develop is perfectly safe.

The incubation period in man may vary from as short as twelve days to over two years. This is said to vary with:

1. The distance the virus must travel in the nerve trunk to the brain.
2. The age. It is shorter in children.
3. General body resistance. According to Koch the virus may lurk in the nervous tissue until resistance is lowered by some other infection or debilitating condition.

Pathology: The presence of Negri bodies in the cytoplasm of cells of the cerebellum are the most commonly sought for pathological evidences of rabies. Herzog, of Chile, has recently revived interest in histological examination of the ganglion nodosum which is said to show evidence of degeneration long before the development of Negri bodies and to be a more consistent finding at any time in the course of the disease.

Diagnosis: Classically, rabies progresses through three stages: excitement, convulsion, and paralysis.

In *dogs* either the first or the latter stage is predominant in each individual case, and the disease is called "furious" rabies or "dumb" rabies.

Furious rabies has a prodromal period of one to two days in which the most noticeable change is in the disposition of the dog. A good natured animal may become irritable and surly, while a bad tempered one may unexpectedly begin to crave attention, fondling and licking its owner's hands. Frequently dogs become restless and wander off at this stage. An abnormal appetite may be seen in which sticks, stones, and hairs are chewed and swallowed. When the period of excitement occurs, the peculiarities mentioned are emphasized and the animal is recognized as "mad." He may run aimlessly through the countryside, sometimes for many miles, snapping at other dogs and at people in its way. The growl may change to a thin whine. After one to ten days, if the dog has not died of exhaustion or other injuries, the paralytic stage appears with progressive weakness of the legs and a staggering gait. The jaw may drop in paralysis with bloody froth drooling from the mouth. He is frequently unable to raise his head, cannot bite, and death occurs with paralysis of the muscles of respiration.

Dumb or *paralytic rabies* is simply a more virulent form of the disease in which paralysis as just described is present from the beginning of the illness.

The diagnosis may be aided by:

1. Confinement for ten days. As a rule, if rabid, the dog dies at the fourth or fifth day.
2. Examination of the stomach contents.
3. Microscopic examination of the brain for Negri bodies or for ganglion pathology.
4. Subdural or intracerebral innoculation of laboratory animals with brain tissue emulsion.

In *man* we must differentiate the early stages from tetanus, foreign body aspiration, poliomyelitis, encephalitis, meningitis, reaction to antirabic vaccine therapy, hysteria, and delirium tremens.

There are, as a rule, no symptoms during the incubation period. Symptoms are first apparent in the throat muscles with difficulty in swallowing, progressing to fear of painful spasms of these muscles when he tries to take food or water.

As a rule, there are early complaints of dyspnea, marked excitement, apprehension, sleeplessness, and heavy sweating. There is a leukocytosis and a low but steadily rising temperature.

Spasmodic muscular contractions appear on the second or third day. The mind may be clear between convulsions or there may be auditory or visual hallucinations. Death usually occurs during a convulsion on the third or fourth day—either from respiratory paralysis, cardiac failure, or cerebral apoplexy. Occasionally there is lingering for a few hours into the paralytic stage, but the average duration of a course of human rabies is three days.

Prevention and Treatment: Once rabies has developed, there is no treatment other than sedation. There is on record no case which has lived.

After a bite we should confine the dog for observation. If it is necessary to destroy him, the head should not be damaged.

The classical routine for local treatment of bites, and the one still advised by most workers is fuming nitric acid either

as a swab or by dropper. This causes extensive scarring and encourages wound infection. Shaughnessy and Zichis argue that this heroic treatment is effective but not necessary and have experimentally shown that irrigation with 20% soft soap solution is just as efficient as, and possibly more so, than the chemical cauterization. Their results indicate that either method in the first two hours will prevent two out of three cases from developing the disease. The wound should never be sutured.

The Pasteur treatment usually consists of fourteen daily injections of an emulsion of fixed virus. Dr. S. W. Bohls, of the State Department of Health, advocates longer courses up to forty doses when the bites are severe or are above the shoulders. Dr. T. C. Terrell, of Dallas, has also used much longer courses plus blood serum from patients recently finishing treatment.

All observers agree that treatment should be started at once, if:

1. The dog is obviously rabid.
2. The dog cannot be found.
3. The dog was killed soon after the bite, for this may have occurred before Negri bodies developed in the brain.
4. The laboratory reports the tissue unsatisfactory to examine because of decay.
5. The bite is above the shoulders.
6. Rabid saliva gets into a fresh wound.
7. A child's face has been licked by a dog known to be rabid.

Occasionally varying degrees of ascending myelitis with paralysis develop following vaccine therapy, but with Semple's phenol killed virus, the mortality has been reduced to 0.01% and the paralysis is usually transient in those that recover.

With the Pasteur treatment the mortality in a series of 69,541 persons bitten by rabid dogs was 0.23%; without treatment the mortality is about 16%, so one should never allow the possibility of reaction to influence his giving the vaccine in doubtful cases.

Immunity following following treatment lasts about one year.

General Prophylaxis: Rabies is a disease which can be definitely wiped out by control of the canine population which

furnishes 90% of the source of the disease and is almost the 100% responsible reservoir.

Control may be established by the same public health measures as previously described for Great Britain, namely quarantine, muzzling, and licensing. There have been no deaths from rabies since 1903 in the British Isles, but there have been 3,000 deaths in the United States since that date.

In summary, it might be said that rabies is a comparatively minor public health problem to all except the man who has just been bitten by a rabid dog.

On the 19th of November a case of rabies was admitted to our hospital. Both the parents and the patient were extremely coöperative, and we were able to obtain an unusually detailed history covering the prodromal period of the illness. I thought it might be of interest to give an account of the entire case in more detail than is generally seen in the literature.

Case Presentation: J. A. B., a fifteen-year-old white male.

Saturday, 16 November

He felt fine all day but noted with surprise that he had no appetite that night. He went to bed at 12:00 and to sleep without restlessness.

Sunday, 17 November

2:00 A.M. He awoke with his body and the bedclothes wet with perspiration. He had never experienced this before. There were no chills, and he did not feel feverish.

4:00 A.M. He awoke again in a heavy sweat.

8:00 A.M. He got up feeling fine and did his chores. He had no appetite; refused breakfast, lunch and dinner, but drank large amounts of coffee and water. He was restless throughout the day.

10:00 P.M. The restlessness had disappeared, and he went to sleep without trouble.

12:00 MIDNIGHT. He awoke in a heavy sweat, describing the covers as "soaked."

Monday, 18 November

6:00 A.M. He awoke feeling restless and thirsty.

8:00 A.M. He got up feeling well and ate a large breakfast. He did all of his work without feeling bad at all and ate a heavy lunch.

3:20 P.M. He told his sister he "felt funny." He was a little tired and dizzy, but continued to go about as usual.

6:00 P.M. He had no appetite at dinner and did not feel well.

10:00 P.M. He went to bed in a restless mood and had difficulty going to sleep, says he "counted the minutes, sheep, etc."

12:00 MIDNIGHT. He awoke, wet with perspiration; was thirsty, but did not get up for water.

2:00 A.M. He still could not sleep. At this time he noted he was having trouble breathing. He was sweating heavily. He got out of bed to awake his father, but fell to his knees with dizziness. When he tried to drink a glass of water, he stated that his "head flew back as if someone had pushed it." He was frightened and felt "pale and weak." Back in bed he continued to breathe heavily and could not sleep the rest of the night. He had no chills and did not feel hot.

6:15 A.M. When given milk of magnesia, he had a hard time swallowing it but at last managed by sucking and breathing at the same time.

11:00 A.M. He was seen by his family doctor who found the boy apprehensive and excited with a temperature of 101°. There was no nuchal rigidity or headache. His strength was good, and there was no disturbance of equilibrium. He complained primarily of irregular, deep breathing. When given water, he became excited, hesitant, and would take the cup almost to his lips, then draw his head back. At last he was able with considerable difficulty to drink by sucking and blowing the water. The impression, however, was principally that of dyspnea and fear of choking while struggling for breath.

1:00 P.M. He was admitted to the hospital with a temperature of 99°. He was described on admission as "apprehensive, excited, dyspnic." There was no complaint of pain, no cough, or no excessive salivation. At this time he had no difficulty swallowing saliva, but became more disturbed when water was offered to him and eventually refused it entirely. A physical examination was completely negative with the exception of:

1. Pain in the left arm where he had been kicked by a calf a few days before—began in hand and moved toward the shoulder with no lack of control or strength.
2. Widely dilated left pupil, but both pupils reacted well to light and accommodation. No nystagmus or squint. Knee jerk 4+ with clonus on the left; 1+ on the right. Babinski was questionable, but somewhat more active on the left. Abdominal and scrotal reflexes were absent.
3. The only suggestive laboratory results were a leukocytosis of 11,650 with normal differential, and a specific gravity of 1.035.

In retrospect this picture seems clear enough, but to illustrate the confusion we had four different diagnoses with a question in front of each.

5:00 P.M. We felt that we had established a diagnosis of rabies. The boy was extremely coöperative. He was hyperalert and was able to remember even the most insignificant details of events in the past week. He was highly excited. By now the pupils were equal and regular; his strength was bilaterally equal; knee jerks were bilaterally equal, 4+ with clonus and were often voluntary; biceps 2+; radial 1+; abdominal

and scrotal reflexes were now present, rated at 2+. Babinski negative. No nuchal rigidity was present. Rhomberg was negative.

Wednesday, 20 November

No change was noted during the night. He was given 180 cc. of water by the teaspoonful and stated that he "didn't know water was so good." He had several attacks of dyspnea when he tried to sit up in bed.

10:00 A.M. Temperature 99^4. Other than hyperexciteability and occasional attacks of dyspnea, this patient was in no distress. One of the staff doctors who had seen him briefly expressed doubts as to the diagnosis. He was then amazed at the extreme reaction—fear and screaming, with general muscular spasm—exhibited when a glass of water was offered the boy.

It was noted that it was not so much the fear of water which upset him as it was the fear of something cold. For example he was given a warm sponge bath and several hundred cc. of warm water to drink—both without difficulty.

8:00 P.M. Temperature rose to 101^2 and aerophobia became more pronounced. When the door was opened and the slightest draft was felt, he became wildly aggitated, flinging himself beneath the sheets. If the observer were to blow gently on his hand or foot, he would jack-knife up in bed, every muscle rigid.

10:00 P.M. The picture was now changing rapidly. During the morning he had been mentally clear and unusually acute in his recall; he now began to have visual hallucinations, although he was well oriented as to time and place, and to the people about him. His speech was completely unrestrained, with wild flights of ideas. He waved his hands in jerky, irregular movements and shook his head from side to side. There were no convulsions—only the same type of sudden jack-knife movement, head and feet leaving the bed as if sitting up, wild-eyed, awakening from a bad dream. He would have moments of apparent calm and would tell his brother of something he wanted done for him because "he wouldn't be here tomorrow." He had never been told the diagnosis or prognosis. He had no paranoid tendency or ideas of reference. At one time he asked why we did not tie him down. There was no unusual amount of salivation at this time.

11:00 P.M. He was becoming more difficult to control and would try to leave the bed. He violently refused food and liquids in any form. His ideas were becoming more fixed. There was a good deal of sex content to his raving—babies, marriage, and invitations to the nurses were a major portion of his thought. An erection appeared which was maintained until death. He was aware of his surroundings and the identity of people in the room.

All reflexes were now hyperactive, with clonus. No true nuchal rigidity was present, but the sternocleidomastoid groups were almost constantly taut with voluntary effort. The pupils were completely dilated but still

reacted to light. Babinski reflex was negative. The B.P. was 170/70/20 while at rest. He was wet with perspiration.

11:30 P.M. He became vindictive and aggressive; began to express paranoid ideas, accusing members of the family of playing tricks on him; stated he would get even. He wanted a gun so he could shoot at people who could be heard walking past in the hall. He kicked and lashed out at attendants and relatives, tore off the bed light and bell cord. However, he was coöperative when an attempt was made to help him in any way and took all medications willingly. At one time he leapt out of bed and made a spasmodic attack on his brother. The movements were quick and catlike with no restriction of motion. Equilibrium was good.

His lips began to twitch even when he lay quietly. The fingers and wrists twitched, and he would intermittently double up in a tremendous muscular spasm of the whole body, then suddenly relax. The whole picture was one of extreme, uncontrolled cerebral agitation.

12:00 MIDNIGHT. The patient became a little quieter and was not so sensitive to or aware of his environment as earlier in the afternoon. Drafts, noises, or the sight of water no longer upset him. However, if water were brought he would slap it away.

Thursday, 21 November

1:00 A.M. Excessive salivation began for the first time, and he began to spit on the floor. Small amounts of bloody foam appeared at the corners of the mouth.

1:30 A.M. He became quieter, stated he was going to die, and wanted to see his mother. Immediately after this he had his first convulsion, and then repeated it several times in the next hour. He was salivating excessively.

2:30 A.M. The convulsions were now less violent but were at closer intervals.

4:00 A.M. He complained of his tonsils being so large they "stopped up his throat," then went back to sleep. It was noticed that his jaws were rhythmically opening and shutting.

5:30 A.M. He awoke and had an extremely violent convulsion, thrashing steadily with his feet; hands and forearms were flexed and held to the chest. This went on for several minutes.

5:50 A.M. He leapt to his knees and vomited 200 cc. of foamy, red vomitus, clasped his arms to the abdomen as if in pain, then lay down slowly in bed. His jaws were opening then clamping shut with blood tinged froth covering the lips to the corners of the mouth. Respiration became irregularly shallow with long lapses. Heart action was imperceptible after 5:50 A.M.

6:00 A.M. Declared dead.

Therapy employed: (1) Penicillin in solvecillin 100,000 U. B.I.D. begun on admission and was continued throughout the course, total of 300,000 Units.

(2) He was sedated with nembutal suppositories, morphine gr. ¼ prn., and amytal gr. 3½ during convulsions.

The patient, family, and neighbors were closely questioned as to a possible source of infection. Three possibilities were mentioned:

(1) Seven to eight months ago a small stray puppy played with all the children and the parents. It was very affectionate and playful—nipping, running, and hiding, and licking their hands. The patient received the worse bite of all from the animal—on the middle finger of his right hand. He told me that he immediately dipped it in kerosene and washed it under the pump whereupon it healed without difficulty. The dog did not seem ill, but was unfortunately run over by an automobile the same day.

(2) A month ago a skunk was seen tearing and biting viciously at the wires of the pig pen as if trying to get at the animals. The boy's father says that he thought the skunk was crazy. The boy shot it, handled it, but waited a day before skinning and curing the hide.

(3) One of the cows had been sick a week before the onset of the patient's symptoms. This was diagnosed as pneumonia by the veterinarian whom the boy helped by holding out the animal's tongue when medicine was given. It is still alive and well.

I believe we can discount the last possibility, but there could be a good deal of argument about which of the first two contacts was rabid.

At necropsy the positive findings were:

Gross:

1. Congestion of vessels of the pia mater.
2. Small amount of frothy fluid in the bronchi.
3. Scattered areas of hemorrhagic appearing tissue on section of the liver.
4. A recent hemorrhagic area 1 cm. in diameter on the surface of the left kidney, extending through both cortex and medulla.

Microscopic:

1. Marked congestion and edema of all sections of the brain. The ganglion cells showed various stages of degeneration and necrosis and there was moderate proliferation of glial cells throughout.
2. Passive congestion and cloudy swelling of the kidneys with lumina of tubules filled with albuminous material. The glomerular tufts were swollen.
3. Moderate congestion and cloudy swelling of the liver.

In summary we have presented a typical case of rabies which includes all the classic symptoms of the disease.

They were: Prodromal symptoms of sweating and restlessness, later inability to swallow or catch breath. The second day brought on frank hydrophobia, aerophobia, mental excitement, erections, and excessive salivation. By the third day there was delirium, hallucinations, and violent convulsion ending in death.

The possible sources of infection were a dog bite, six to seven months previously, or an intimate contact with a dead, but quite possibly rabid, skunk.

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BLOOD COAGULATION AND ITS CLINICAL MODIFICATION WITH ANTICOAGULANTS*

ROBERT M. MOORE

As a preliminary to the consideration of anticoagulant drugs it is well to review in some detail the modern conception of coagulation. In all at least six biological substances are believed to be involved in the normal clotting of blood. The process can be outlined somewhat as follows: by the action of *thromboplastin,* and in the presence of *calcium ions*, *prothrombin*, which is inactive, is converted into active *thrombin.* Thrombin, an enzyme, then acts upon the soluble *fibrinogen* of the plasma to convert it into insoluble *fibrin*, the threads of which then enmesh the solid elements of the blood with the result that a clot is formed. To repeat, in the presence of calcium ions thromboplastin activates prothrombin to thrombin, and the thrombin accomplishes the conversion of fibrinogen into insoluble fibrin. Thus of the six substances named, thrombin and fibrin are products of precursors whereas the remaining four substances can be considered to be the primary factors.

Thromboplastin (or thrombokinase) is a fat-soluble phospholipid present in all tissues and liberated upon tissue injury. Among tissues especially rich in thromboplastin are lung, brain, and blood platelets. The essential defect in hemophilia, a deficiency in thromboplastin, is due, it is thought, to an abnormal stability of the blood platelets.

Ionized calcium is an essential factor in normal coagulation. Calcium is always present in blood in an ionized form except in such freak conditions as oxalate or fluoride poisoning or overdosage with citrate. Oxalate precipitates the calcium. Fluoride or citrate binds it into a very weakly dissociated or slightly ionized compound. Aside from these unusual possibilities a low serum calcium is never a causative factor in hemorrhagic

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disease. In hypoparathyroidism, for example, the serum calcium may be less than half the normal value and yet coagulation remains normal.

Prothrombin, the third primary factor, is a carbohydrate containing protein, formed chiefly in the liver but also in the bone marrow. Its production is governed by vitamin K, the fat-soluble naphthaquinone which was discovered by Dam and his associates and is known as the antihemorrhagic or coagulation vitamin. Prothrombin may be dangerously decreased in the plasma in vitamin-K deficiencies, and particularly when in hepatitis, obstructive jaundice or biliary fistula the vitamin K, though perhaps still plentiful in the intestine, is not absorbed because of the relative absence of bile salts from the intestine. The oral administration of bile salts and vitamin K, or in some instances only of bile salts, remedies this prothrombin deficiency. Furthermore, the intravenous administration of vitamin K is an antidote for the prothrombin deficiency resulting from overdosage with dicumarol.

The fourth primary factor in blood clotting is *fibrinogen*, a solution globulin of the plasma. It may be greatly decreased in liver damage but rarely to a point to cause bleeding. A congenital lack or absence of plasma fibrinogen has been described but is also a rarity.

Thus of the four primary factors in coagulation only prothrombin is apt to be deficient pathologically to a degree giving rise to hemorrhage. Thromboplastin, ionized calcium and plasma fibrinogen are present in amounts sufficient for normal clotting with the rarest exceptions.

It should be noted that the *blood platelets* have not been included among the primary factors in clotting. Platelets are not necessary to coagulation, though, as one source of thromboplastin, they have been incriminated in the prolonged clotting time of hemophilia where the platelets have been found to possess an abnormal stability. Platelets are believed to be associated chiefly with clot retraction and with protection and repair of the capillary wall. Their reduction in purpura is associated with the prolonged bleeding time in that condition, the platelet reduction apparently depriving an abnormally

deteriorating capillary wall of their protective and reparative action.

Among substances possible of use to prolong clotting are the salts such as oxalate and citrate which bind calcium and certain other salts which affect other clotting elements. Among substances of biological nature which prevent or retard coagulation are hirudin of the leech, heparin, certain snake venoms, peptone, the sulphur containing amino acid cysteine, and dicumarol which is found in spoiled sweet clover. There is evidence that peptone and the snake venoms act by interfering with thromboplastin liberation whereas the others exert their action by blocking at some point the prothrombin-thrombin mechanism.

In contrast, certain other substances are known to hasten coagulation. Among them is the hormone adrenalin; also tissue extracts rich in thromboplastin. The venoms of some species of snakes are powerful coagulants just as others have been listed for their anticoagulant action. Again, repeated injections of citrate incites an overproduction of coagulant materials within the body.

Many of the agents which lead to intravascular thrombosis in disease states partake of the nature of injury, either injury to the formed elements of the blood or to the capillary wall, and thus can be classed as mechanisms leading to a liberation of thromboplastin. Wounds, bacterial infections and certain cellular toxins may fall within this class. A second group of mechanisms, including polycythemia, dehydration, shock and exposure to cold, appear to invite thrombosis by rendering the peripheral blood more concentrated and viscous. A third group favor slowing and stagnation in the venous return. Decreased respiratory movement, increased intra-abdominal pressure and immobility of the lower extremities are common mechanisms here. In this regard there has been great emphasis in recent years to prevent the abuse of rest in bed.

Among the methods recommended to prevent postoperative thrombosis are the following:

1. Early movement of the extremities; avoiding dependence of the extremities.

2. Avoidance of any constriction about the pelvis and abdomen. For example, the cava or its tributaries can be flattened by abdominal tumors (including the distended bladder) and by the increased intra-abdominal pressure attending intestinal distention or tight abdominal binders. The popliteal veins may be sharply angulated by the traditional Fowler's position and semisitting postures encourage stagnation in the iliac veins.
3. Avoidance of restrictions to respiration; inducing hyperventilation to encourage venous return.
4. Administration of sufficient fluids to prevent dehydration (some urge a diet composed largely of carbohydrates in view of certain evidence that the platelet count and the fibrinogen are raised by a high protein diet).
5. The use of anticoagulants to decrease the tendency for clotting.

Aschoff (1924) in a classical study of intravascular thrombosis found that coagulation was frequently a sequel to the obstruction of the vein by a white thrombus of platelets. Owing to their lower specific gravity the platelets leave the axis or core of the sluggish venous stream to occupy the more slowly moving zone next to the vessel wall. With the reduction of the velocity of flow in this outer zone to a certain critical level the platelets settle upon the vascular walls in a ribbed pattern as when sand is deposited upon the seashore or at a river's mouth. The ribs or ridges are increased in height by the aggregation of fresh platelet masses. Next, the leucocytes, having a lower specific gravity, separate from the red cells and move into the outer currents to cling to, and finally to come to rest upon the platelet masses. Ultimately there is complete blockage of the venous channel, and, as the circulating blood is thus brought to a standstill, there is coagulation en masse of the blood in the vein distal to the plug of platelets and leucocytes.

If Aschoff was correct in this view that thrombosis in the uninjured vein is usually secondary to the obstruction of the vessel by a white plug formed while the blood is flowing, then our need in an anticoagulant is for a factor which opposes the agglomeration of platelets. Unfortunately no such agent has yet been developed for practical use, and to prevent intravascular thrombosis we are reduced to the necessity of choosing

among anticoagulants which act by interfering in the fundamental prothrombin-thrombin mechanism. In view of the essential nature of this mechanism it is small wonder that such anticoagulants are found difficult and dangerous of use.

From a practical standpoint we have at the moment but two anticoagulants available—heparin, a potent antithrombin, and dicumarol, a potent antiprothrombin.

McLean, a pupil of Howell, discovered in 1916 that certain impure extracts of liver inhibited the coagulation of blood. Howell and Holt in 1918 succeeded in obtaining a powerful coagulant from extracts of dog's liver. In 1933 Charles and Scott isolated from beef liver a potent crystalline heparin containing nearly 100 units per milligram. A unit is defined as the quantity which will prevent for 24 hours the clotting of 1 cc. of cat's blood when kept in the cold.

Heparin is a glycoprotein containing sulphuric acid groups and acting as a relatively strong acid. It apparently is a product of the mobile basophil or mast cells of the tissues and is contained in greatest amount in liver, lung, muscle and intestinal wall. Only traces are normally found in the serum, though both Howell and Quick have found heparin to be liberated from the liver into the serum in peptone shock. The anticoagulant effect of heparin is due chiefly to its powerful action in inactivating thrombin, in which respect there is mutual antagonism between heparin and thromboplastin. Heparin action is immediate and marked, though fortunately it is only temporary. Murray and Best (1938) found at the Toronto General Hospital that when the clotting time of man had been raised to 20 minutes by the intravenous use of heparin it returned entirely to normal within an hour when heparin administration was ceased, and that when the clotting time had been elevated to 90 minutes it returned to normal within an hour and twenty minutes after stopping the heparin. de Takats (1946) reports that 50 mgm. intravenous doses have so expended their effect within 4 hours that there is no cumulative action when such doses are given at 4-hour intervals. It is maintained that discontinuation of heparin results in no negative after effect such as abnormal shortening of the coagulation time.

Aside from the cost of heparinization (approximately ten dollars per day) the chief drawback in its use has been the labor of a continuous intravenous drip method. At Toronto Murray and Best established a method which long remained standard of administering heparin in saline in a concentration of 10 units of heparin[1] to 1 cc. of saline and giving this solution by constant intravenous drip at the rate required to increase the patient's clotting time to about three times normal. This requires on the average about 25–30 drops per minute. Such a drip is very tedious to the patient and laborious to the house staff and nurses, especially if continued for more than 48 hours. With the discovery of dicumarol the necessity for longer periods of heparinization has largely disappeared. Moreover, there has been a continued effort to substitute methods less laborious than the intravenous drip even for a 48-hour period. Walker (1945) recommends intramuscular injections at 6-hour intervals and suggests 50 mgm. at each injection. He finds subcutaneous injection too irritating. de Takats prefers an intermittent intravenous administration, giving 50 mgm. each four hours. He appears to have had a large experience with this form of heparinization and to be satisfied with its efficacy, but makes the precautionary recommendation that the clotting time be determined hourly until the effect of this dosage on the particular patient has been demonstrated. In connection with animal experimentation a desire to make one daily dose suffice has lead to extensive trials of heparinization by subcutaneous or intramuscular injection in a retarding medium such as beeswax (Bryson and Cole, 1944), Pitkin's menstruum (Loewe and Rosenblatt, 1944) and Pitkin's menstruum with the addition of a vasoconstrictor (Weiner and Lange, 1947). Pitkin's menstruum is a mixture of gelatin, dextrose, acetic acid and distilled water. To this heparin is added. The dried menstruum is warmed until it liquefies at 80° F. and is injected rapidly through a No. 19 needle. Both Weiner and Lange and Walker recommend the addition of 0.5% chlorbutanol because of the danger of infection. Apparently hematoma formation is frequent.

[1]The unit must not be confused with the milligram. Milligrams per 100 cc. will depend upon the potency of the particular preparation used.

It is my present tendency to use 50 mgm. intramuscular or intravenous injections instead of the intravenous-drip method. The drug is potent and I believe it must be given warily with careful check on the coagulation time attained. With these provisions recent experience has lead more than one to be less fearful of moderate heparinization than of the use of dicumarol. Murray and Best recommended that heparinization never be started until 4–24 hours following operations because of the risk of inviting bleeding into the wound. Just recently I ligated the superficial femoral vein in a young woman with calf thrombosis on the advice of our Medical Service who believed she had just suffered a minor pulmonary embolism. I began heparinization by 50 mgm. intravenous dosage an hour after the operation. Although we had used local anesthesia (0.25% procaine) with no added adrenalin and had exerted particular care to ligate every bleeding point before closing the wound, the following day the wound was distended with a hematoma which caused worry and no doubt prolonged the patient's hospital stay by several days. However, it seems to me that this is a risk one must assume in certain instances. Since immobility favors venous statis it is highly likely that the hours of operation and release from anesthesia carry particular danger of thrombosis or clot propagation in some cases. If heparin is needed it is indicated at once. Some degree of hematoma formation will not be surprising in fresh operative wounds. If excessive spontaneous hemorrhage occurs the antidotes are to discontinue the heparin and to give a blood transfusion. These steps will usually be effective immediately, since heparin effects disappear within the hour. The drug should not be used in the presence of active bleeding and withdrawal of administration usually serves to stop ordinary hematoma formation.

Dicumarol, an anticoagulant found in spoiled sweet clover, was discovered by Link at the University of Wisconsin and later synthesized (1942). Dicumarol delays or prevents the formation of prothrombin.[2] Its advantages over heparin are

[2]Dicumarol affects prothrombin B. the component which is also chiefly affected in vitamin K deficiency. Quick's prothrombin A, which disappears from stored plasma, apparently is of secondary importance both as regards dicumarol and vitamin K.

that it can be given by mouth as a daily capsule and that it is cheap (Segard, 1945). It possesses, on the other hand, distinct disadvantages. It acts slowly and the action recedes slowly, not in an hour as with heparin. A dose of dicumarol given now will not have its full effect upon the clotting mechanism for from 12 to 48 hours. Consequently, if an immediate effect is desired heparinization is still necessary. Furthermore, because of this time lag one can never predict with certainty the extent of dicumarol effect one will have tomorrow or the next day. This must constantly be borne in mind when the clinical effect begins at all to approach the danger level. Even though no more dicumarol be given there may be spontaneous hemorrhage tomorrow. Salicylates enhance the dicumarol effect, whereas the xanthines of coffee, tea, and cocoa retard it. These facts may explain certain otherwise unpredicted results. Since dicumarol depresses the concentration of prothrombin the proper measurement of its effect is not the coagulation time but the prothrombin time of Quick. Unfortunately prothrombin time is a difficult laboratory determination. Clinical pathologists are still debating as to whether it is best performed upon plasma, diluted plasma or whole blood. A control upon a normal person should always be run and the prothrombin time of the patient is expressed in the percentage: time for clotting of the normal divided by time for clotting of the patient. de Takats recommends that sufficient dicumarol be given daily to mtaintain prothrombin time between 50 and 30 per cent normal. Walker recommends the lower level of 20–30 per cent normal. When overdosage results in spontaneous bleeding the antidotes are blood transfusion or intravenous administration of 72 mgm.[3] or more of vitamin K, in addition, of course, to temporary discontinuation of the dicumarol. For proper effect the dicumarol dosage usually recommended is 300 mgm. the first day, 200 the second, and thereafter a maintenance dose depending upon daily prothrobin-time determinations. A combination with heparin administration is commonly used (Holden, 1947).

[3]The standard commercial ampoule for intravenous use contains 72 mgm. and should not be confused with the ampoule of 1 mgm. or less for use in the newborn.

the prolonged coagulation time from heparin being relied upon for 48 hours and then the heparin discontinued as the effect of dicumarol upon the prothrombin time becomes evident. It is stated that there are no ill effects if there is an overlap of a day when there is both the heparin antithrombin effect and the dicumarol antiprothrombin action. However, this matter deserves further study.

I have become convinced that dicumarol must never be used without frequent prothrombin time checks, preferably daily checks and necessarily so until the maintenance dose has been carefully established in the individual patient. Furthermore, the day's dose of dicumarol must never be ordered until that day's prothrombin time has been reported. The natural inclination is for the laboratory to report the prothrombin time late in the day and for the house physician to become overconfident after a few days and order more dicumarol before the report is in. Twice in recent months I have seen serious difficulty arise from this mistake. In one instance resort was made to transfusion when the following day found the prothrombin time had gone off the board. This is the danger in using dicumarol, its action is delayed. If it is stopped with the prothrombin time at 35% normal today, tomorrow the time may be far below 30% at the dangerous level of spontaneous hemorrhage. Furthermore, the dicumarol effect is cumulative. Recently I have been treating a woman with iliofemoral thrombosis with a maintenance dose of dicumarol given five days per week. After three weeks during which the prothrombin time had ranged daily between 50 and 60 per cent, with a surprising proportion of readings at 56 per cent, the resident ordered a capsule of 100 mgm. one day before the laboratory report had been rendered. It came in a few hours later as 45 per cent. No more dicumarol was given but the following day the determination showed a prothrombin time of 30 per cent, the second day 30 per cent and the third day 33 per cent. During this period the patient first developed a fairly large hematoma in a bruise on one arm and then a severe hematuria which disappeared overnight after an intravenous dose of 72 mgm. of vitamin K.

The leech and the hirudin of its buccal glands have been used as anticoagulants for centuries and probably could still be used to advantage with proper controls (Lilienthal, 1938). The sulphur of the thiosulphate radicle is at the moment in use in some places. Bancroft (1938) cites a dose of 10 cc. of 10 per cent sodium thiosulphate intravenously daily as a prophylactic, combined with hydration and a low caloric diet. For a long time thyroid extract has been considered a preventive in some clinics in view of its effect in raising the metabolism and increasing the circulatory rate. However, the efficacy of the dose used within the time allotted is often questioned.

At the moment, therefore, only heparin and dicumarol are in wide use. To my mind the safety of their use depends to some extent upon one's philosophy in anticoagulant therapy. After all, one accomplishes considerable in preventing thrombosis or clot propagation if he assures a situation in which the tendency to clotting does not exceed the normal. To be certain this is being accomplished it is necessary to maintain coagulation values which are measurably below normal. If one can succeed in this, why need he attempt a greater reduction? If with heparin the clotting time can be prolonged to twice normal why aim at three times normal? If with dicumarol one reduces prothrombin time to 50 per cent of the control why need it be reduced to 30 per cent, particularly since in doing so one is forcing a mechanism which is hard to predict to a level of reduction approaching danger? In a limited experience I have not seen a fatal effect from an anticoagulant but I have observed several embarassing predicaments from overdosage which did give rise to concern. Such experiences convince one that these drugs are powerful and that their safe use depends first, upon careful laboratory determination of the effect being obtained, and second, upon attempting only the more moderate reductions.

During recent years a great deal of attention has been given to the ligation of veins to prevent embolism from migration of clot fragments. It is generally agreed that the preferable form of attack is to prevent the occurrence of thrombosis. Constant attention to avoid the various physical and mechanical factors which favor intravascular thrombosis will usually eliminate

the need for more active treatment. However, if one fears thrombosis particularly in a given case an anticoagulant may be used carefully to aid in prophylaxis. Once thrombosis is recognized to have occurred anticoagulant therapy is indicated to minimize clot propagation. Again, the practice of frequent laboratory checks and an attitude of caution are advised.

Finally, it should be mentioned that both digitalis and morphine sometimes act to favor propagation of a pulmonary embolus. When the physician is confronted with a patient suffering an acute attack of dyspnea and chest pain so that embolism is suspected, deferring digitalis and morphine and substituting such drugs as atropine and papaverine which act to relieve vascular and bronchial spasm may be of great benefit in pulmonary embolism and will rarely do harm if the attack proves on further study not to be of embolic origin.

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THE ELECTROCARDIOGRAM IN MENTAL DISEASE

ARTHUR RUSKIN, JEROME RAVEL, AND BRUCE BEARD*

Vago-sympathetic control of the heart renders it peculiarly liable to psychosomatic disturbances. The nervous reflex implications of cardiac pain and dyspnea, as well as the various mechanism disorders, in particular—ectopic beats and paroxysmal tachycardias, are well known. Psychoneurotic patients have symptoms referable to the cardiovascular system as often as those implicating any other major system in the body.

Previous studies of electrocardiographic changes in cases of mental aberration have been restricted as to number, kind of cases studied, and interpretation. In 1935, Graybiel and White noted that some young individuals with neurocirculatory asthenia presented diphasic or negative T leads in the limb leads of the electrocardiogram. The same group later (1941) re-emphasized the occurrence of these findings particularly in asthenic individuals without heart disease, and in the semi-erect position, as a result of lowering of the diaphragm and positional changes of the heart, as well as possible sympathetic nervous influences.

The well-known tendency of psychoneurotic patients to rapid and sighing types of respiration has caused some authors (Thompson, 1943) to interpret the finding of S-T segment depressions and T negativities in these cases as due to the hyperventilation syndrome. We shall note our objections to this interpretation in the discussion of our results.

Wendkos (1944) has published extensive observations on the influence of vago-sympathetic imbalance, and the effects of vago- and sympatho-mimetic drugs, with particular reference to the occurrence of negative T waves in lead IVF. He has also emphasized the day-to-day variability of T_4 in these cases from positive to negative, and vice versa. Many of his patients belonged to the psychoneurotic category.

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In a previous report from this institution (Ruskin, McKinley, and Decherd, 1945) the finding of short P-R intervals (0.10–0.12 sec.) in a significant number of psychiatric, as well as hypertensive and thyrotoxic, cases was explained as a sympatheticotonic trait. A recent German study (Meyer and Billman, 1940) of 100 depressive cases notes the occurrence of the following "functional" EKG abnormalities: T_1 negative (in 1 of 3 tracings) in 1 case; T's flattened, especially in leads II and III, in 6 cases; prolonged P-R interval in 4 cases. They noted the reversal of T wave abnormalities in 5 of the 7 cases within several days. No S-T segment depressions were reported by them.

Method

We reviewed the electrocardiograms of a 100 severe mental cases, hospitalized on the Neuropsychiatric Service, and thoroughly studied to rule out any organic disease. The ages of the patients varied from 14 to 50, older cases being excluded because of possible latent coronary sclerosis. In most cases only 1 or 2 electrocardiograms were available; if more had been taken, more abnormalities would have been undoubtedly uncovered. We omitted from the study all tracings following shock therapy, drug administration, or hyperventilation, as well as those showing a heart rate over 100 per min., since all these conditions may themselves produce like electrocardiographic changes. S-T depressions were measured from the T-P interval as the isoelectric line. T waves were considered low when less than 1 mm. (0.1 millivolt) in height.

Results

The major EKG findings for the entire group of 100 cases are listed in Table I.

1. *Defective Personality Cases.* There were 9 cases of personality defects, some labeled as of the constitutional psychopathic inferior (C.P.I.) type, with or without morphine, alcohol, or isonipecaine (demerol) addiction, and others classed as cases of simple adult maladjustment. None of them showed even suggestive EKG abnormalities, except, possibly, one C.P.I. case who had a deep, 4 mm., Q_4 (Table I).

2. *Psychoneurotic Cases.* Of 39 sypchoneurotic patients, usually of the anxiety, and some of the conversion, type, 24 showed suggestive differences from the average norms (Table I). The most significant EKG aberrations were S-T

TABLE I*

Diagnosis	No. Cases	P–R 0.10–0.12 sec.	S–T Depression of 1 mm.	T_1, T_2 or T_4 Low	T_1, T_2 or T_4 Flat	T_1, T_2 or T_4 Diphasic	T_1, T_2 or T_4 Negative
Personality Defects	9	....	....	.....	.....	.....	....
Psychoneuroses	39	3	9	7(+2)	1(+1)	2(+1)	2
Pathological Depressions	22	3	....	6(+2)	3	.....	2
Functional Psychoses	30	5	6	1(+1)	.....	2	....
Total	100	11	15	14(+5)	4(+1)	4(+1)	4

*T wave changes occurring in the same cases as more marked T changes are counted in parentheses. Detailed analysis in text.

segment depressions, typically in leads II and III, of 1 mm. or more in any 1 lead, which occurred in 9 cases (Fig. 1a). These electrocardiograms would ordinarily be considered to indicate definite evidence of myocardial damage by our present criteria. In 2 of these cases follow-up tracings showed reversion of the S-T segment to the isoelectric level; this paralleled the improvement in the mental state. In 1 of the 2, a 33-year-old woman with severe conversion hysteria, the Master two-step test was positive (Fig. 1b) at the time of normalization of the electrocardiogram, 3 weeks after admission. S-T depressions of 0.5–1 mm. were present in 1 or more leads in 9 other cases.

T waves were low in 7 cases: 2 in lead I, 1 in lead II, 2 in leads I and II, and 2 in lead IVF; secondarily (i.e.), in addition to more marked T wave changes in other leads in the same cases, they were low in lead I in 2 other cases. T_4 was flat in 1 case, and T_2, secondarily, in another. Diphasic T waves in lead IVF were present in 2 psychoneurotic individuals, and negative T waves in the same lead in 1 case. An additional case showing only low T_1 and T_2 in the horizontal position of the patient, presented orthostatic tachycardia, with

marked depressions of the S-T segments and inversion of the T waves in leads II and III in the sitting position (Fig. 2). Logue et al. (1944) present similar instances in cases of vasomotor instability and angina pectoris.

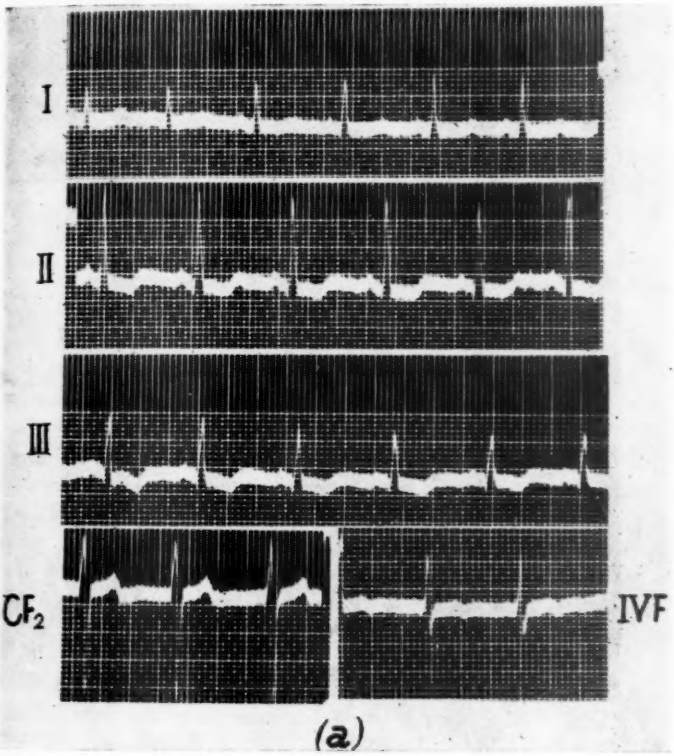

FIG. 1a. Electrocardiogram of 33-year-old female with a conversion psychoneurosis, and without organic disease; taken in the horizontal position. Depressed S-T_2 1 mm.+, depressed S-T_3; T_1 low, T_2 and T_3 negative, T_4 diphasic; P-R 0.11 sec.

Prominent P waves of the high peaked type were noted in lead II in 1 case, and in leads II and III in another. P-R intervals of 0.10–0.12 sec. were present in 3 cases, and one of 0.21 sec. in 1 case of the sypchoneurotic group. One showed

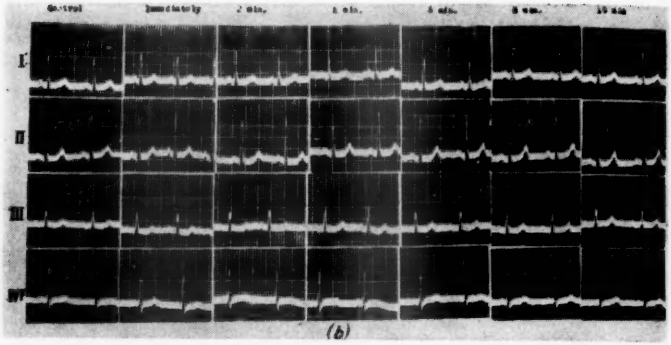

FIG. 1b. Master 2-step test in same case. 3 weeks later, mental state much improved. Normal control; P-R 0.13 sec. Depressed S-T_2 and S-T segment flattened T_4 on exercise. Consistent with coronary insufficiency (functional?).

a 4 mm. deep Q_3, which was 50% of the highest limb lead QRS. Two cases presented premature ventricular, and one A-V nodal ectopic, beats in the electrocardiogram; others may have been missed in the tracings. Two cases had known frequent attacks of paroxysmal auricular and ventricular tachycardia, respectively; in each case associated with an apparently normal heart, and with significant S-T segment depressions between attacks. In one patient the sinus rate varied with emotional excitement from 88 to 167 beats per minute, the S-T depressions in the 3 limb leads being most marked at the higher rate, and the P-R interval varying accordingly from 0.11 to 0.09 sec. The most common combined EKG findings were, typically, S-T depressions plus short P-R intervals (Fig. 1a). Many other combinations were the rule rather than the exception.

3. *Pathological Depression Cases.* The 22 cases in this group comprised simple, acute, and recurrent depressive states, without severe psychotic components. S-T depressions of 0.5–1.0 mm. in any 1 lead occurred in 7, usually in leads II and III. In 2 cases of mixed anxiety psychoneurosis and acute depression, classed with the former group, S-T segments were depressed more than 1 mm.

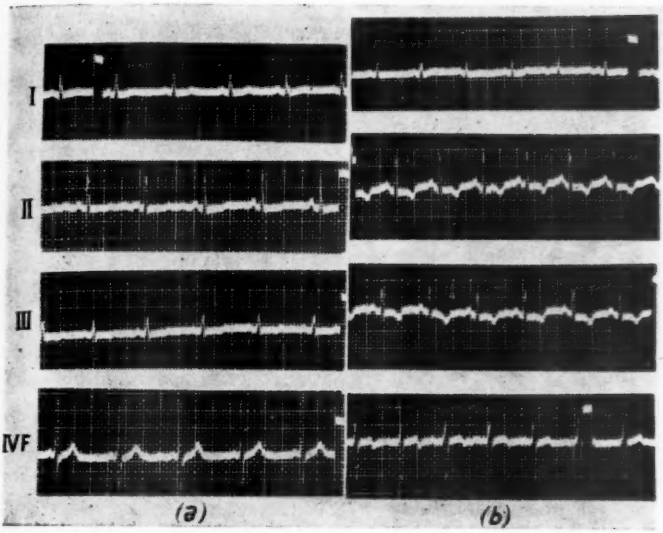

FIG. 2a. Electrocardiogram of 31-year-old female, with conversion hysteria, no organic disease; taken in the horizontal position. P-R 0.12 sec., S-T_2 and S-T_3 slightly depressed, T_3 and S-T_2 low.

FIG. 2b. Same case, electrocardiogram taken in sitting position. Sinus tachycardia, markedly depressed S-T_2 and S-T_3, flat T_1, negative T_2 and T_3, diphasic to low T_1. Orthostatic changes, only slightly positional (fluoroscopy).

T waves were low in lead I in 4 cases, secondarily in 2 others, and in lead IVF in 2 more. They were flat in lead I and IVF in 1 case each, and in leads I, II, and IVF in 1 other case. Two cases presented negative T waves in lead IVF. One of these was a 38-year-old man in severe depression superimposed on a chronic anxiety psychoneurosis. His first EKG showed negative T_4 and low T_1 waves (Fig. 3a). Two weeks later, with improvement in the mental state, T_4 became low upright and T_1 higher (Fig. 3b).

A short P-R interval of 0.10–0.12 sec. was noted in 3 instances. One case presented ventricular premature beats, with frequent bigeminy, and no known predisposing causes other than his illness (simple depression).

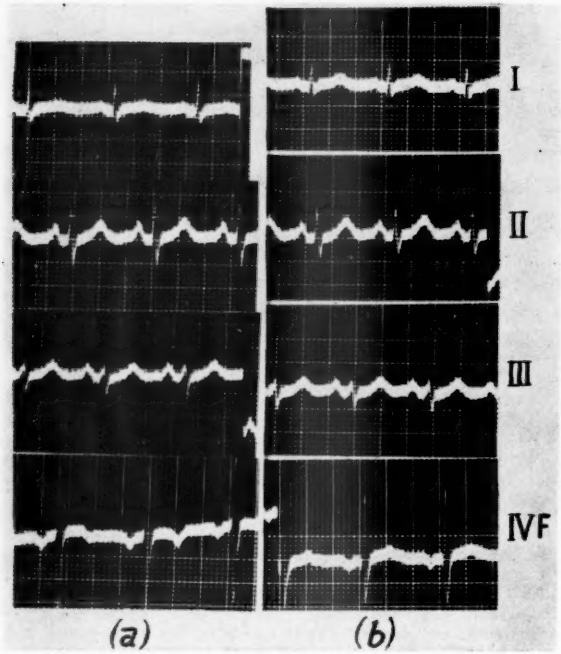

FIG. 3a. Electrocardiogram of 38-year-old man with severe depression superimposed on a chronic anxiety psychoneurosis; no organic disease. Low T_1, negative T_4.

FIG. 3b. Same case 2 weeks later, mental state improved. Higher T_1, low upright T_4; favorable(?) changes in EKG.

4. *Functional Psychoses Group.* Cases of schizophrenia (11), manic-depressive sypchosis (manic phase) (4), and involutional depressive psychosis (15) presented essentially the same EKG findings. S-T depressions of 1 mm. or more in any 1 lead were noted, chiefly in leads II and III, in 6 cases, 3 of involutional depression, 2 of schizophrenia, and 1 of manic-depressive psychosis. Less marked depressions, 0.5–1.0 mm. in depth, occurred in 7 others, similarly distributed. The T wave was diphasic in lead IVF in 2 cases of involutional psychosis. The P-R interval was 0.10–0.12 sec. in a total of 5 psychotic cases, 3 involutional and 2 schizophrenic; in 1

case of schizophenia it was 0.21 sec. The P waves were high and pointed in lead II, in association with a markedly depressed S-T_2, in 1 chronic severe schizophrenic. Atrio-ventricular rhythm (transitional?), with flat P_2 and negative P_3, was present in 2 cases of schizophrenia. Another showed a 4 mm. deep Q_3.

Discussion

It is to be noted that the EKG findings described above are rather uniformly present in all types of mental illness, suggesting a common denominator from the standpoint of their cardiac somatic component. The 9 cases of C.P.I., maladjustment, or drug addiction were evidently least emotionally upset—hence, perhaps, the lack of suggestive EKG findings. Alcoholics, without pellagra, were similarly found to be free from EKG abnormalities by Feil (1936).

The other data must be evaluated in terms of what is found in the average healthy young adult group, as recently promulgated by Stewart and Manning (1944) and Graybiel et al. (1944). Many of our findings differ so markedly from the norms that they need no statistical proof of their significance. P-R intervals of 0.10–0.11 sec. are found in only 2% of normal young adults; in our psychiatric series they were found in 6% of the cases. S-T_2 and S-T_3 depressions of 1 mm. or more likewise occur in 0.4% of healthy young men (Graybiel et al., 1944); they constituted 15% of our cases. Excluding lead III, T flattening or negativity occurred, chiefly in lead IVF, in 12% of our cases; this is 30 times the normal incidence (Graybiel et al., 1944).

Low voltage T waves occurred in the significant leads, I, II, and IVF, in 14% of our patients. Their causes, like those of low voltage of all the R waves, which occurred twice, are so numerous, that, despite this high incidence, their significance is questionable. This finding appears to be more characteristic of the psychoneurotic and simple depressive groups, however, than the psychotic. The incidence of high pointed P waves, prolonged P-R intervals, deep Q waves, slightly depressed S-T intervals, and ectopic rhythms, probably did not exceed their average occurrence in healthy young adults. The

2% incidence of A-V nodal rhythm may be no exception. On the other hand, that it occurs under conditions of vagal stimulation, as on carotid sinus pressure, is well known. One of us (A. R.) has noted it in the vaso-vagal syncope of venipuncture; others (Loftus et al., 1945) in nymphomania. Hence, its presence in the 2 schizophrenic patients may possibly be due to nervous reflex effects.

A few studies have already linked neurocirculatory asthenia, or, more properly, psychoneurosis with symptoms referable to the cardiovascular system, with inversions of the T waves in the various leads of the electrocardiogram. Thus, Logue et al. (1944) noted negative T waves in leads I, II, and IVF in 5% of such cases, a figure exactly comparable to ours (Table I). They also reported prolongation of the P-R interval in 7 of 74 cases, reversible by atropine in 3, not seen in our data, and mentioned S-T depression in only one case. We have noted this and other changes, interlinked, so frequently, that we cannot agree with their conclusion that there is no characteristic electrocardiogram in neurocirculatory asthenia. Indeed, we can go further and state, that suggestive EKG findings frequently exist not only in cardiac neuroses, or psychoneuroses in general, but in all types of psychiatric disturbances.

The mechanism of cardiac and electrocardiographic psychosomatic manifestations is undoubtedly complex and has to be considered from the following angles:

1. *Emotional factors:* The association of EKG changes with emotional instability, in cases without any evidence of organic heart disease, has been emphasized in this country by Wendkos (1944). Loftus et al. (1945) reported 1 case of low T waves in lead I and II following intense anxiety, and 1 case of A-V nodal rhythm following sexual excitement, among 41 mentally ill patients, who otherwise presented no EKG abnormalities.

One of the most significant studies from the standpoint of etiology of the reported EKG changes is that of Mainzer and Krause (1940), who noted as a result of the preoperative emotion of fear, temporary S-T depression and T flattening and

inversion surprisingly like those denoting coronary insufficiency. Anesthesia and operation influenced the electrocardiogram in these cases comparatively little or not at all. The authors quote Dunbar's report of a fatality on the operating table, before the induction of anesthesia, and explain it, similarly, on the basis of sudden marked reflex diminution of coronary blood flow.

2. *Endocrine factors.* The EKG changes noted by Scherf (1938) in menopausal and hypo-ovarian states, and relieved by nitroglycerine and the follicular hormone, may be due in great part, as the author admits, to the associated neurosis. The influence of hypo-ovarian states on the EKG is apparently mild (slight S-T and T depressions), and has not been widely confirmed. The frequently associated asthenic halitus, and almost constantly present emotional instability must be considered in the evaluation of these EKG changes. While testosterone has been proposed for the therapy of cardiac pain associated with the male menopause, even less is known of the effects of this drug and syndrome upon the EKG. States of severe emotional upset are undoubtedly associated with hyperadrenalemia, which may or may not be sufficient to cause transient relative coronary insufficiency. There is some evidence that conditioned reflex hypersecretion of pitressin may occur in certain emotional states (Pickford, 1945), followed, as is well known, by diuresis, but there is no proof that it is marked enough to exert its powerful coronary vasoconstrictor effect (Ruskin, in press).

3. *Hyperventilation factor.* Marked hyperventilation, which is frequently seen in anxious neurotic individuals, undoubtedly can produce EKG changes in the direction of T wave depression, whether or not alkalosis, tetany, or anginoid pains result. Thompson (1943) presented neurotic cases that responded to acute induced hyperventilation by marked S-T depression in leads II and III, and T negativities. This work has not been generally confirmed. Some of that author's control tracings seem to be abnormal to start with. There is the possibility that the emotional tension and exertion associated with hyperventilation may produce relative coronary insufficiency. To

this may be added the criticisms of Chamberlain (in the discussion of Thompson's paper) that marked lowering of the diaphragm may produce negative T waves in lead III and even lead II, under these circumstances, and that 2 of his own cases responding in this fashion to hyperventilation later died of proven coronary sclerosis. Scherf and Schlachman (1947) explain the lowering of voltage following hyperventilation entirely in terms of positional changes, which would, of course, be exaggerated in asthenic neurotics. In any case, hyperventilation was not present in any of our cases, nor in those of Logue et al. (1944).

4. *Dehydration and avitaminosis factors.* Many mental cases are sufferers from starvation, vomiting, dehydration, and vitamin deficiencies. In alkalosis due to prolonged vomiting marked S-T depressions in leads II and III have been noted (Lawrence and Allott, 1943). Dehydration alone may cause ST-T depressions (Camman, 1939). Beriberi has been associated with a short P-R interval (Aalsmeer and Wenckebach, 1929) and even T wave inversions (Keefer, 1930). Pellagra presents similar abnormalities, and S-T depressions, at times (Mainzer and Krause, 1940; Feil, 1936). It is possible that these factors were not entirely excluded in our study.

5. *Vago-sympathetic imbalance.* The occurrence of reflex diminution of coronary flow in a variety of conditions, from fear, pain, and anesthesia (Mainzer and Krause, 1940), and intra-abdominal disease (Swalm and Morrison, 1940), to experimental distensions of the esophagus, stomach, and gallbladder (Kalk and Kolsch, 1939; Gilbert et al., 1940) is well established. The slowing of the sino-auricular rate and atrioventricular conduction, as well as diminution of coronary blood flow (Dietrich and Schwiegk, 1933), as a result of vagus stimulation, and the opposite results of heightened sympathetic tone, are also well-known. There is evidence, in both human and animal subjects, that vagal overactivity predisposes to depression of the S-T segment and reversion of the T waves (Kalk and Kolsch, 1939; Manning et al., 1937; Bohnenkamp, 1923).

Sympatheticotonia may be responsible for the relatively short P-R intervals in some of our cases (Ruskin et al., 1945);

it has been suggested as a cause of high T waves occasionally seen by other observers in neurosis (Logue et al., 1944), as well as in fear electrocardiograms (Mainzer and Krause, 1940). A markedly increased cardiac rate and output resulting from sympathetic overactivity may conceivably cause relative coronary insufficiency despite dilatation of the coronary arteries. Graybiel and White (1935) emphasized the nervous factor in the production of S-T and T depressions in conditions such as neurocirculatory asthenia and thyrotoxicosis, though later (1941) they placed greater emphasis on positional changes of the heart and diaphragm. Wendkos (1944) claimed that in some of his cases of emotional instability—vagal, and in others sympathetic, tone predominated, and suggested various autonomic drug tests for their classification. That is admittedly difficult and uncertain.

The lability of the ST-T portion (Nachschwankung) of the electrocardiogram under nervous and emotional, as well as cardiac musculo-vascular, imbalance, is getting better and better established. The finding of a positive Master 2-step test (Fig. 2b) in a young woman, almost certain not to have coronary atheromatosis, weeks after the hysterical storm and its attendant EKG abnormalities have passed away, is of great interest in this connection.* In other cases of mental disease the exercise tests have shown either no change or higher T waves in the EKG, provided coronary disease could be reasonably excluded. Serial studies of this type both during and after severe stages of mental conflict are needed to evaluate the demonstrated EKG findings in their psychosomatic aspects.

Summary and Conclusions

1. Suggestive electrocardiographic aberrations exist in cases of neuroses and the functional psychoses. They are both variable and reversible, thus indicating their functional origin.

2. Some variations from the mean, such as the short P-R interval, are of interest as indicating autonomic nervous system imbalance.

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*Two similar instances have been noted since the submission of this paper.

3. Others, such as depressed S-T segments and flat, diphasic, or inverted T waves are of sufficient frequency and significance as to raise the questions of the presence of coronary insufficiency and of myocardial damage, or the impropriety of present-day criteria for the identification of the latter.

4. Emotional and endocrine factors, the hyperventilation syndrome, positional changes of the heart and diaphragm, vago-sympathetic influences, and possible relative inadequacies of coronary blood flow, are discussed in connection with the production of the above EKG findings.

5. In view of the tremendous incidence of mental disease and emotional instability in patients with and without heart disease, and of the above data, our electrocardiographic criteria of myocardial damage may need radical revision.

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Thompson, W. P.: The Electrocardiogram in the Hyperventilation Syndrome. Am. Heart J., 25:372, 1943.

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Calling Attention To

Items of Possible Interest to Friends of Our Effort
March, 1947

1. Symposia: Abstracts are available of excellent antibiotic symposium held February 1, 1947, under auspices of the National Institute of Health; the reports deserve publication in full. R. H. Goetz, M. M. Suzman, and L. McGregor offer interesting symposium on hypertension (*South African Med. J.*, 21:2–23, January 11, 1947). Symposium on Army pathology appears in tribute to J. E. Ash (*Mil. Surg.*, 99:361–719, 1946). G. M. Badger and E. Stedman discuss molecular asymmetry and biological action (*Nature*, 159:194, February 8, 1947). Important physiological surveys covering all recent work from growth to defense mechanisms coming soon (*Ann. Rev. Physiol.*, Vol. 9, 725 pp., 1947). Recent symposia of New York Academy of Science include Lymph (*Proc.*, 46:679–822, 1947); Blood Groups (46:883–992, 1946); Brain and Body Weight in Man (46: 993–1122, 1947); Proteins and Protein Hydrolysates in Nutrition (47:241–374, 1946); Physio-Chemical Mechanism of Nerve Activity (47:375–602, 1946); Antibiotics (48:31–218, 1946), and Folic Acid (48:255, 1946). Note discussion on overactivity of adrenal cortex (*Proc. Roy. Soc. Med.*, 40:35, 1946), and ditto on birth control (*ibid.* p. 51).

2. Physiology: W. L. Lipschitz and E. Stokey discuss various mechanisms of antidiuresis (*Am. J. Physiol.*, 148:259, 1947). T. Sollmann notes 15-day survival in cold of neuromuscular reflexes after somatic death (*ibid.* p. 299). J. Auer and H. Krueger describe peristaltic and antiperistaltic phenomena in gut (*ibid.* p. 350). W. Raab and R. J. Humphreys find that sympathetic ganglia contain much epinephrin and related compounds (*ibid.* p. 460). R. Gesell and others further discuss electrotonic theory of nervous integration (*ibid.* p. 515). D. H. Smyth finds much acetate metabolism in liver related to fat metabolism, about 3 m. mol./kg./hr., slightly less than alcohol (*J. Physiol.*, 105:299, 1947). P. Hugh-Jones discusses effect of limb position on muscle force (*ibid.* p. 332). J. H. Gaddum and L. G. Goodwin suggest that liver sympathin is norepinephrin or tyramine (*ibid.* p. 357). E. Mellanby claims that vitamin A regulates position and activity of osteoblasts and osteoclasts (*ibid.* p. 382). Note also S. B. Wolbach's neat article on Vitamin A and skeletal growth (*J. Bone Joint Surg.*, 29:171, 1947). D. Nachmansohn and others discuss general role of acetylcholine in nerve and muscle conduction (*J. Neurophysiol.*, 10:11, 1947). C. R. Giudice reports on potassium in cephalic fluids (*Rev. Neurol. Argentina*, 11:105, 1946). E. E. Ecker and others find low serum protein disposes toward low complement titer in infectious diseases (*J. Clin. Invest.*, 25:800, 1946). M. Prinzmetal and others find toxic factor in blood in burn shock (*ibid.* p. 781). M. Bjorneboe and others (Copenhagen) report on role of plasma cells as antibody producers

(*J. Immunol.*, 55:121, 1947), F. Schlenk and M. J. Waldvogel note enzymes reducing pentose concentration from purine and ribose nucleotides and sides (*Arch. Biochem.*, 12:181, 1947). R. W. Gerard and others find choline esterase not essential to nerve conduction (*Proc. Soc. Exper. Biol. Med.*, 64:106, 1947).

3. PHARMACOLOGY: R. H. Williams and others correlate chemical structure with antithyroid action (*Am. J. Med. Sci.*, 213:198, 1947). R. A. Peters and H. Cullumbine discuss mustard gas action (*Nature*, 158:149, February 1, 1947). E. H. Barany and E. S. Jensen discuss anticonvulsant drug action (*Arch. Internat. Pharmaco.*, 72:2, December, 1946). G. Schwartzman and A. Fisher describe antibacterial action of irradiated pyridoxamine (*J. Biol. Chem.*, 167:345, 1947). A. B. Corkill and J. F. Nelson report that post pituitary extract counteracts insulin by causing epinephrin secretion from adrenals (*Med. J. Austral.*, 1:130, February 1, 1947). C. H. A. Walton and J. A. K. MacDonell review antihistamine drugs (*Canadian Med. Asso. J.*, 56:162, 1947). R. L. Mayer and others recommend pyribenzamine aerosel administration in antihistamine therapy (*Proc. Soc. Exp. Biol. Med.*, 64:92, 1947). M. F. Guyer and P. E. Claus note inhibition of mitosis by urethane (*ibid.* p. 3).

4. FURTHERMORE: J. B. Conant offers pleasant historical approach to understanding science illustrated from R. Boyle's *Touching the Spring of the Air*, London, 1660 (*Am. Scientist*, 35:33, 1947). C. Gutierrez-Noriega discusses Cervantes' medical psychology (*Rev. Neuro-Psi.*, 9:107, 1946). B. J. Anson pleasantly contemplates fantasy in medicine (*Quart. Bull. Northwestern Univ. Med. School*, 21:1, 1947). A. M. Master is pessimistic about increase in incidence of acute coronary artery occlusion (*Am. Heart J.*, 33:135, 1947). E. Brodman and others describe statistical methods useful to medical librarians (*Bull. Med. Lib. Asso.*, 35:7, 1947). H. Eagle discusses inactivation of various penicillins by serum (*J. Exp. Med.*, 85:141, 163, 1947). Our W. Levin emphasizes symptomatic character of anemias (*Texas St. Med. J.*, 42:573, 1947). Our J. McGivney notes importance of anorectal infections (*ibid.* p. 587).

APRIL, 1947

1. SPRING FEVER BOOKS: On the moralizing front P. Wylie offers hectic *Essay on Morals* (Rinehart, N.Y., 204 pp., $2.50). H. C. Link fuzzily dogmatizes on *The Rediscovery of Morals* (Dutton, N.Y., 223 pp., $2.50). L. duNouy pulls a mystic Alexis Carrel in *Human Destiny* (Longmans, N.Y., 289 pp., $3.50). and I. Edman pleasantly describes a *Philosopher's Quest* (Viking, N.Y., 275 pp., $3.00). B. M. Duncum's *Development of Inhalation Anesthesia* is the British story, with much on apparatus (Oxford, 640 pp., 35s). A. R. McIntyre offers important *Curare: Its History, Nature, and Clinical Use* (Univ. Chicago, 220 pp., 1947, $5.00). D. Rynin edits A. B. Johnson's noteworthy *Treatise on Language* (Univ. California, 1947, 456 pp., $5.00). R. E. Coker edits 14 notes on Southern problems, including D. E. Lilienthal's "Moral Re-

sponsibility of Research" (Univ. North Carolina, 1946, 229 pp., $3.00). J. P. Greenstein offers *Biochemistry of Cancer* (Academic Press, N.Y., 1947, 396 pp., $7.80). H. Selye's *Encyclopedia of Endocrinology* comes along with Vol. 7 on *Ovarian Tumors* (Richardson, Montreal, 1946, 427 pp., $5.00). J. M. D. Olmsted writes another pleasant biography in *Charles-Edouard Brown-Sequard: 19th Century Neurologist* (Johns Hopkins, Balt., 1946, 253 pp., $3.00). B. M. Bernheim discusses *A Surgeon's Domain* (Norton, N.Y., 253 pp., $3.00). H. B. Friedgood describes *Endocrine Function of the Hypophysis* (Oxford Press, N.Y., 1946, 437 pp., $4.50). D. J. Leithauser discusses *Early Ambulation and Related Procedures in Surgical Management* (C. C. Thomas, Springfield, Ill., 1946, 241 pp., $4.50). J. E. Moore offers *Penicillin in Syphilis* (C. C. Thomas, Springfield, Ill., 1947, 329 pp., $5.00). M. Pijoan and C. H. Yaeger issue *Commonly Used Drugs* (C. C. Thomas, Springfield, Ill., 1947, 198 pp., $3.75). T. D. Spies describes *Experiences with Folic Acid* (Yearbook, Chicago, 1947, 110 pp., $3.75). A. A. F. Peel offers *Diseases of the Heart and Circulation* (Oxford Press, N.Y., 1947, 419 pp., $9.75). H. T. Pledge summarizes *Science Since 1500* (Philosophical Library, N.Y., 1947, $5.00).

2. Cytology: E. Undritz and E. Rothlin have new evidence supporting J. H. Wright's theory (*Virchow's Arch. Path. Anat.*, 186:55, 1906) of platelet orgin from bone marrow megacaryocytes (*Helv. Med. Acta.*, 13:595, 1946). I. Wallgren describes pale granular substance of cell and relation to structure (*Acta. Path. Microbiol. Scand.*, 23:415, 1946). G. I. Roskin further notes cytologic changes in malignant tumors under action of schizotrypanum endotoxin (*Bull. Exp. Biol. Med. USSR.*, 22:18, 1946). C. Brun and others study hydrodynamics of semipermeable tubes in relation to glomerular kidney function and find contraction of vas efferens must occur to account for clearance findings (*Acta. Physiol. Scand.*, 12:321, 1946). S. W. Wajda proposes possible hemopoiesis from striated muscle cells (*Nature*, 159:254, February 22, 1947).

3. Neurology: J. W. Kirklin and others discuss causalgia (*Surg.*, 21: 321, 1947). M. A. Kennard reviews autonomic interrelations with somatic nervous system (*Psychosomat. Med.*, 9:29, 1947). W. Ashby suggests that disturbances in distribution pattern of carbonic anhydrase in brain may accompany mental disorder (*J. Nerv. Ment. Dis.*, 105:107, 1947). F. Feldman and others describe ambulatory electroshock therapy (*ibid.* p. 171). L. Orbeli reviews effects of extracortical factors on CNS function (*Am. Rev. Sov. Med.*, 4:206, 1947). M. L. Barr discusses basis of heart pain (*Rev. Canad. Biol.*, 5:602, 1946). O. A. M. Wyss and others localize medullary inspiratory center sensitive to afferent vagal stimuli (*Helv. Physiol. Pharmacol. Acta.*, 4:495, 1946). W. J. O'Connor discusses control of urinary secretion by pituitary pars nervosa (*Biol. Rev. Cambr. Philosoph. Soc.*, 22: 30, 1947). Note excellent symposia on working capacity and on fitness for work (*Occupational Med.*, 2:531, 566, 1946).

4. Therapeutic Notes: R. Bessiere and H. P. Gerard report promise in paresis with Na p-hydroxy m-aminophenyl arsenite (*Presse. Med.*, 12:

130, February 22, 1947). E. Anderson and J. A. Long find insulin secretion stimulated by high glucose levels, and that AP growth hormone inhibits insulin secretion (*Endocrinol.*, 40:92, 98, 1947). G. K. Moe and others report clinical usefulness of tetraethyl ammonium bromide (10 mgms/Kg. IM) by blockade of autonomic ganglia (*Am. J. Med. Sci.*, 213: 315, 1947). H. L. Segal and others further discuss value and safety of anion exchange resin (Polyamine formaldehyde resin) in management of peptic ulcer (*Gastroenterol*, 8:191, 199, 202, 1947). M. Nickerson and L. S. Goodman note possibility of "dibenamine" (N, N-dibenzyl-B-chloroethylamine) as an adrenergic blocking agent (*J. Pharmacol. Exp. Therap.*, 89:167, 1947). W. H. Feinstone and others note possible value of 2-butoxy-5-aminopyridine in tuberculosis (*ibid.* p. 153). G. A. Levy offers thorough study of arsine poisoning (*Quart. J. Exp. Physiol.*, 34:47, 1947). Our A. Ruskin and G. M. Decherd describe use of thiamine HCl (300 mgmc. IV) as useful agent to measure circulation time from arm to tongue (*Am. J. Med. Sci.*, 213:337, 1947).

MAY, 1947

1. TEXAS CITY DISASTER: Experience demonstrated successful application to civilian casualties of escheloned military medical principles, especially through effective co-operative team-work of skilled specialists in speciality organized hospital. General points: First-aid with rescue squads; preliminary dressing with general practitioners who directed evacuation to specialty organized hospital; rapid diagnosis and sorting by specialty teams; careful surgery, open drainage, liberal use of plasma, whole blood, penicillin, tetanus and gas-gangrene antitoxin, fluid balance control, careful anesthesia, and detailed records. Now planning rehabilitation clinic (See H. A. Rusk, Rehabilitation. *Ann. Int. Med.* 26. 386/47). Staff put two emergency teams into field within 30 minutes after explosion, received 408 casualties, lost 16 (chiefly severe cranial injuries), transferred 90 to convalescence within 48 hours, discharged 120 within 6 days, and handled rest in routine. With large pool of 76 residents, 320 medical students and 250 nursing students, it was a text-book demonstration. Splendid aid from Red Cross, Army, Navy, American Legion, Boy Scouts, nurse groups, Dallas Blood Bank, local merchants. Blast equal to atom bomb without radioactivity. Full account will appear in *Texas Reports on Biology and Medicine*.

2. BOOKS: Notable result of G. Sarton's influence is J. B. Conant's Terry Lectures *On Understanding Science: An Historical Approach* (Yale Press, New Haven, '47, 160 pp., $2). How about considering ethical significance of science? With usual British bias and much of value on apparatus. B. M. Duncum offers *The Development of Inhalation Anesthesia with Special Reference to the Years 1846–1900* (Oxford Press, '47, 656 pp., 35 s). Interesting title is B. Evans' *The Natural History of Nonsense* (Knopf, N.Y., '46, 294 pp., $3). G. B. Webb and D. Powell offer *Henry Sewell, Physiologist and Physician* (Johns Hopkins, Balt., '46, 200 pp., $2.75). A. B. Luckhardt recommends E. Andrews' *History of Scientific*

English: The Story of Its Evolution Based on a Study of Biomedical Terminology (R. R. Smith, N.Y., '47, 342 pp., $7.50). N.Y. Academy of Medicine Committee reports on *Medicine in the Changing Order* (Commonwealth, N.Y., '47, 258 pp., $2). J. Samuels writes *Die Hormonversorgung des Foetus* (Brill, Leiden, '47, 320 pp., $3.50). G. Pincus edits *Recent Progress in Hormone Research: Proceedings of Laurentian Conference* (Academic Press, N.Y., '47, 406 pp., $7.50). A Szent-Gyorgyi offers *Chemistry of Muscular Contraction* (Academic, N.Y., '47, 150 pp., $3.50). M. D. Kamen writes *Radioactive Tracers in Biology* (Academic, N.Y., '47, 300 pp., $5.50). A. N. Whitehead returns in *Essays in Science and Philosophy* (Philosophical Library, N.Y., '47, 300 pp., $4.75). E. J. Lund summarizes *Bioelectric Fields and Growth* (Univ. Texas Press, Austin, '47, 400 pp., $6). R. S. Stevenson revives *Morell Mackenzie: The Story of a Victorian Tragedy* (Schuman, N.Y., '47, 312 pp., $5). H. J. Muller, C. C. Little and L. H. Snyder collaborate on *Genetics, Medicine, and Man* (Cornell Press, Ithaca, '47, 171 pp., $2.25). Neat is A. Fleming's *Chemotherapy Yesterday, Today and Tomorrow* (Marmillan, N.Y., '47, 39 pp., 50c). F. Y. Wiselogle edits 2 vol. *Survey of Antimalarial Drugs 1941–1945* (Edwards, Ann Arbor, '47, 2457 pp., $30). W. H. S. Jones offers *Philosophy and Medicine in Ancient Greece* (Johns Hopkins, Balt., '47, 100 pp., $2). M. H. Fisch issues fine review of E. J. and L. Edelstein's *Asclepius: A Collection and Interpretation of the Testimonies* (Johns Hopkins, Balt., '45, 2 vols., $7.50) and adds much (*Bull. Hits. Med.* 20: 712/46). M. F. A. Montagu edits *Studies and Essays in the History of Science and Learning offered in homage to George Sarton* (Schuman, N.Y., '47, 596 pp., $1).

3. Also Noteworthy: W. A. Hagan, H. R. Cox, W. H. Feldman, I. F. Huddleson, H. N. Johnson, R. A. Kelser, J. V. Klauder, K. F. Meyer, C. D. Stein, W. H. Wright offer symposium on relation of diseases in lower animals to human welfare (*Ann. N.Y. Acad. Sci.* 48: 351–576/47). E. J. Cohn, J. Stokes, G. R. Minot and C. A. Janeway offer symposium on therapeutic blood fractions (*Ann. Int. Med.* 26: 341–376/47). T. O. Gray, J. A. Hobson, G. Ostlere, A. Gillis give symposium on tubocurarine and curare (*Brit. Med. J.* 1: 444–451, Apr. 5/47). J. Field well discusses cell respiration and fermentation in relation to narcosis (*Anesthesiology* 8: 127/47). T. D. Fontaine and Co. report on tomatin, antibiotic from tomato possibly useful vs. fungi (*Ann. Biochem.* 12:395/47). H. Lowenbach and M. H. Greenhill think lactic acid is common effective agent in aiding depressive states (*J. Nerv. Ment. Dis.* 105: 343/47). E. R. Hart recommends salicylamide as safe effective analgesic (*J. Pharmacol.* 89: 205/47). D. F. Marsh and A. J. Davis compare antihistaminic cmpds. (*Ibid.* 234). So does R. L. Mayer (*Ann. Allergy* 5: 113/47). G. Schloss suggests renal tubules produce renin (*Helv. Med. Acta.* 14: 22/47). L. Claesson and N. Hillarp show formation of estrogenic hormones from cholesterol in ovaries (*Acta. Physiol. Scand.* 13: 113/47). Our C. M. Pomerat, E. H. Frieden and E. Yeager report further on reticulo-endothelial immune sera in blocking doses (*J. Infect. Dis.* 80: 154/47).